1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2, Amendment 1, Administrative Changes 3, 4, 5, 6, 7, 8 and 9 and Amendments 2, 3, 4, 5 and 6 and Amendment 7 for Poland

AbbVie Number/ Investigational Product:	Adalimumab
Date:	26 May 2015
Development Phase:	3
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.
EudraCT Number:	2007-006494-90
Investigator:	Multicenter (Investigator information on file at AbbVie).
Sponsor:	<u>European Union Countries</u>: AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany <u>Non European Union Countries</u>: AbbVie 1 North Waukegan Road North Chicago, IL 60064
Emergency Contact:	[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is the following:

- Administrative Changes 8 and 9 were incorporated.
- Add subject visits through Week 408 throughout the protocol.

  Rationale of Change: Extension of this open-label study is necessary to allow for continued collection of long-term safety and efficacy information and provision for study to continue until local regulatory approval and reimbursement.
- Add the Complaint and Product Complaint definition to Section 6.0, Section 6.2.1 and Section 6.2.2 as well as the reporting requirements for Product Complaints.
- Section 8.1.5, Interim Analysis, has been updated.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix U.

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3.0 Introduction

Crohns Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is heterogeneous

with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohns disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohns disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and 133 subjects continued in a 32-week double blind segment. Clinically significant

improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigators Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease. The subject population will consist of subjects who participated in and successfully completed the

M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigators discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigators discretion. For a detailed description of the study please see Section 5.0.

Safety Information

In 2008 FDA issued an early communication about an ongoing safety review of TNF blockers and the development of lymphoma and other cancers in children and adolescents.

As of the December 2009 FDA Pediatric advisory committee, it was noted that in general, adverse events seen in studies submitted for the JIA indication were similar to those in the adult population, both in type and frequency.

Due to the relatively rare occurrence of these cancers, the limited number of pediatric patients treated with TNF blockers, and the possible role of other immunosuppressive therapies used concomitantly with TNF blockers, the FDA was unable at that time to fully characterize the strength of the association between using TNF blockers and developing a malignancy. Product labeling for all anti-TNF agents now includes language regarding the risk of pediatric malignancies as requested by the FDA.

Furthermore, in November 2011 the FDA requested that all manufacturers of TNF inhibitors undertake a coordinated effort to better understand the risks for malignancies that develop in patients who are 30 years of age and younger at the time of diagnosis. Reporting requirements for these events can be found in Section 6.1.5 Adverse Event Reporting. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience with adalimumab can be found in the current Investigator's Brochure.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow

treatment. A disease flare is defined as an increase in the Pediatric Crohns Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI score obtained at the subjects previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohns treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohns specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 408 weeks (approximately 8 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

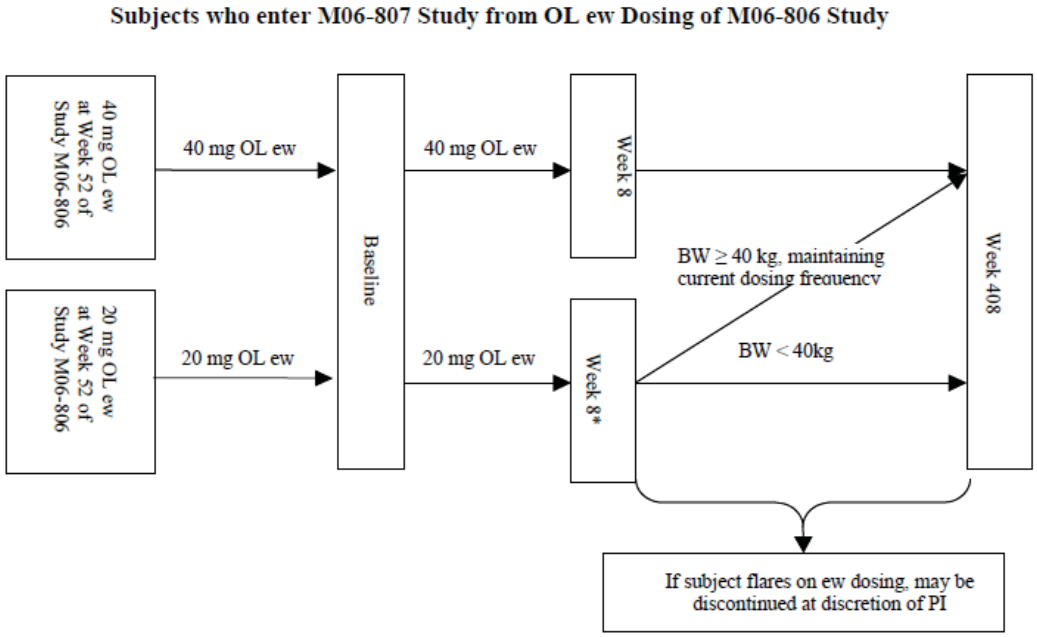
- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohns Disease.
- All applicable local reimbursement procedures are completed.

Sites will be notified once these criteria are met.

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

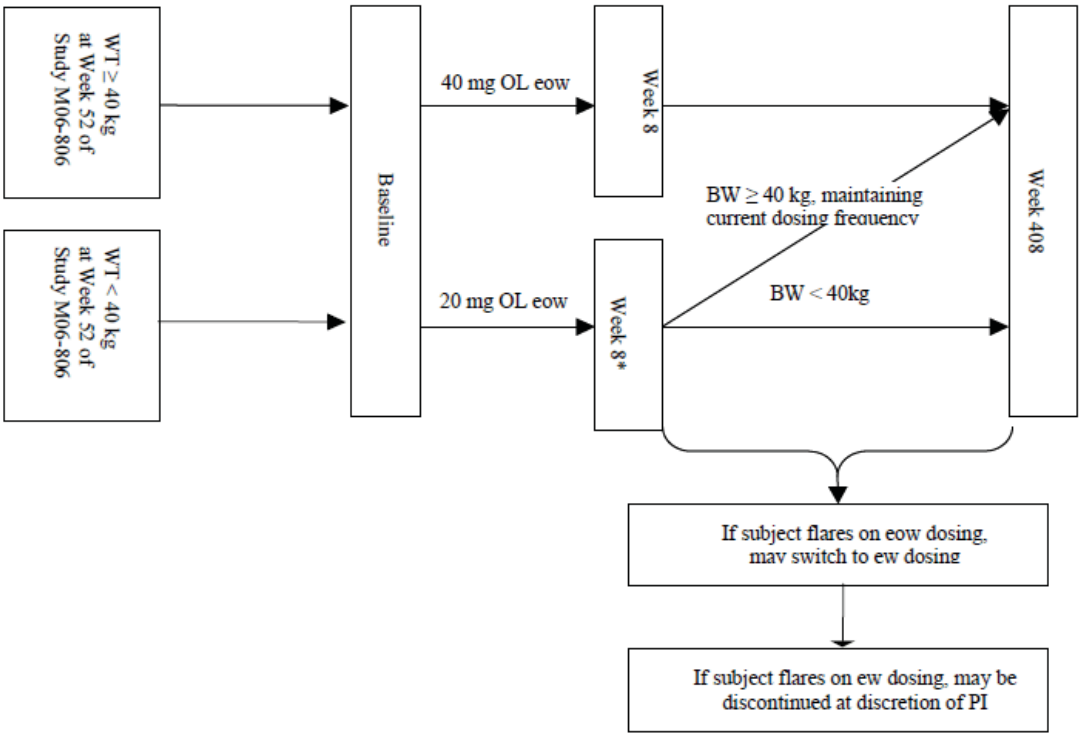
A schematic of the study design is shown in Figure 1 (prior to Amendment 4) and in Figure 2 (after Amendment 4).

Figure 1. Study Schematic



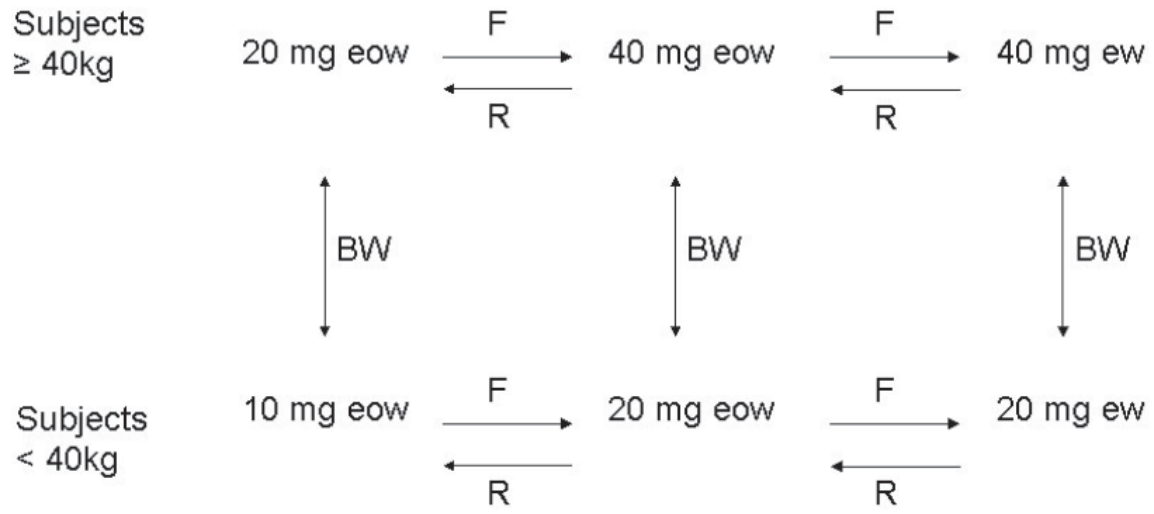
*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Figure 2. Dosing Schematic After Amendment 4



F: Subjects who have a disease flare may be switched to the next higher treatment level.

R: Subjects who responded to their current treatment may be switched to the next lower treatment level at the discretion of the investigator after discussion with the medical monitor. Response is defined as a) a ≥ 15 points decrease in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) a ≥ 15 points decrease in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate.

BW: Subjects with an increase in body weight to ≥ 40 kg may increase their dose to the next higher level at the discretion of the investigator after discussion with the medical monitor. Subjects with a decrease in body weight to < 40 kg may decrease their dose to the next lower level at the discretion of the investigator after discussion with the medical monitor.

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.
2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:
   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner
4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subjects parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.
5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subjects diary.
6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.
7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohns disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.
3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma-in-situ of the cervix.
4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.
5. Subject with known, symptomatic obstructive strictures.
6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.
7. Subject who has short bowel syndrome as determined by the Investigator.
8. Subject who is currently receiving total parenteral nutrition (TPN).
9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.
10. Female subject who is pregnant or currently breast-feeding.
11. Subject with a history of clinically significant drug or alcohol abuse in the last year.
12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.
13. Subject with any prior exposure to Tysabri (natalizumab).
14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the AbbVie Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the AbbVie Medical Monitor identified in Section 7.0

In addition for patients age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate CRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate CRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information

including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate CRF pages.

5.2.3.2 Concomitant Therapy

Adjustments of Crohn's related concomitant treatments, including Crohn's related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohn's related antibiotics or Crohn's related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the AbbVie Medical Monitor. In addition, subjects may be able to initiate or reinitiate Crohn's related treatments, following eight (8) weeks of exposure to open-label adalimumab. Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and total parenteral nutrition (TPN) during the study should be discussed with and approved by the Medical Monitor prior to use.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg	5 mg/week
	≤ 10 mg	2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), and any investigational agent are prohibited during the study (see Appendix L).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Inclusion/exclusion criteria	X									
Informed consent	X									
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X
TB testing (PPD or QuantiFERON-TB Gold)[e]							X			
Urinalysis[f]	X[a]	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X	
ANA	X[a]			X						
Anti-dsDNA[g]	X[a]			X						
PCDAI	X[a]	X	X	X	X	X	X	X	X	X
CDAI[h]	X[a]	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[i]	X[a]			X	X		X		X	

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X
X-ray for bone age[j]	X[a]						X			
Serum bone markers	X[a]				X		X		X	
PK Blood Sample[k]					X		X		X	
Anti-adalimumab blood levels (AAA)[k]					X		X		X	
Adverse events[l]	X[a]	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Inclusion/exclusion criteria										
Informed consent										
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X	X	X		X		X		X	
Vital signs[c]	X	X	X		X		X		X	
Physical exam	X	X	X		X		X		X	
General LAB[d]	X	X	X		X		X		X	
TB testing (PPD or QuantiFERON-TB Gold)[e]	X				X				X	
Urinalysis[f]	X	X	X		X		X		X	
Erythrocyte sedimentation rate	X	X	X		X		X		X	
CRP		X			X		X		X	
ANA		X			X				X	
Anti-dsDNA[g]		X			X				X	
PCDAI	X	X	X		X		X		X	
CDAI[h]	X	X	X		X		X		X	
IMPACT III Questionnaire[i]		X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X	X	X		X		X		X	
X-ray for bone age[j]		X			X				X	
Serum bone markers[j]		X	X		X		X		X	
PK Blood Sample[k]	X		X		X		X		X	
Anti-adalimumab blood levels (AAA)[k]	X		X		X		X		X	
Adverse events[l]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336	Week 348 Call	Week 360
Inclusion/exclusion criteria													
Informed consent													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X		X		X		X		X		X		X
Vital signs[c]	X		X		X		X		X		X		X
Physical exam	X		X		X		X		X		X		X
General LAB[d]	X		X		X		X		X		X		X
TB testing (PPD or QuantiFERON-TB Gold)[e]			X				X				X		
Urinalysis[f]	X		X		X		X		X		X		X
Erythrocyte sedimentation rate	X		X		X		X		X		X		X
CRP	X				X		X		X		X		X
ANA					X								
Anti-dsDNA[g]					X								
PCDAI	X		X		X		X		X		X		X
CDAI[h]	X		X		X		X		X		X		X
IMPACT III Questionnaire[i]	X		X		X		X		X		X		X

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336	Week 348 Call	Week 360
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X		X		X		X		X		X		X
X-ray for bone age[j]					X				X				X
Serum bone markers[j]	X		X		X		X		X		X		X
PK Blood Sample[k]	X		X		X		X		X		X		X
Anti-adalimumab blood levels (AAA)[k]	X		X		X		X		X		X		X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X		X

Table 1. Study Activities (Continued)

Activity	Week 372 Call	Week 384	Week 396 Call	Week 408/ Early Term	Unsched Visit	70-Day Follow-Up Call
Inclusion/exclusion criteria						
Informed consent						
Previous and concomitant medications	X	X	X	X	X	
Urine pregnancy test[b]		X		X	X	
Vital signs[c]		X		X	X	
Physical exam		X		X	X	
General LAB[d]		X		X	X	
TB testing (PPD or QuantiFERON-TB Gold)[e]		X		X		
Urinalysis[f]		X		X	X	
Erythrocyte sedimentation rate		X		X	X	
CRP		X		X	X	
ANA				X		
Anti-dsDNA[g]				X		
PCDAI		X		X	X	
CDAI[h]		X		X	X	
IMPACT III Questionnaire[i]		X		X	X	
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	

Table 1. Study Activities (Continued)

Activity	Week 372 Call	Week 384	Week 396 Call	Week 408/ Early Term	Unsched Visit	70-Day Follow Up Call
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)		X		X	X	
X-ray for bone age[j]				X		
Serum bone markers[j]		X		X	X	
PK Blood Sample[k]		X		X	X	
Anti-adalimumab blood levels (AAA)[k]		X		X	X	
Adverse events[l]	X	X	X	X	X	X
Dispense study drug		X			X[m]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.

b. Performed on all females of child bearing potential – Urine pregnancy test at all study visits.

c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.

d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.

e. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192, 240, 288, 336, 384 and 408/ET. No annual TB test should be done at Week 408 or at ET if already done at Week 384 or later.

f. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 – 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

g. If an ANA result is positive, anti-dsDNA will be performed automatically.

h. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.

i. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408/ETC and unscheduled visits.

j. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.

k. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.

Table 1. Study Activities (Continued)

l. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).

m. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228, 252, 276, 300, 324, 348, 372 and 396 in order to collect any safety information from the subject as illustrated in Table 1.

The visit window for all scheduled visits is ± 7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institutions IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of

legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 408/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subjects casebook from the previous study (M06-806). They will not be required to be captured in the subjects casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subjects M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix O) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

TB Testing

For subjects with a negative test at Screening visit from parent study (Study M06-806), an annual PPD or QuantiFERON-TB Gold re-test will be required. If one of the annual tests

has a positive test result, the matter should be discussed with the medical monitor prior to starting any prophylaxis.

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, 240, 288, 336 and 384. TB testing should not be done at Week 408 or at the ET visit if a test was done at week 384 or later.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case must be discussed with the AbbVie Medical Monitor.

For the PPD test:

- The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The absence of induration should be recorded, as "0 mm," not "negative."
- If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.
- If QuantiFERON®-TB Gold (or equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or equivalent) result is indeterminate, this should be considered a positive test result and the case must be discussed with the AbbVie Medical Monitor.

In the event both a PPD test and QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test.

Newly initiated prophylactic treatment should be captured in the source documents and on the concomitant medications page in the CRF. Prior therapy should be captured in the appropriate medical history CRF.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of the PPD skin test and the CXR and has to give his/her opinion about the eligibility of each subject to continue in the study. This opinion must be documented in writing in the subject's source documents.

All subjects with a positive PPD need to be approved for continuation in the trial by both the Czech pulmonologist and the AbbVie Medical Monitor and all such subjects need to receive prophylaxis for latent TB. Under no circumstances can a subject with a positive PPD result and no prior history of treatment for active or latent TB be allowed to continue in this trial.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 - 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the sites local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured as indicated in Table 1. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5 - 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohns Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix G. Instructions for completing the PCDAI score is located in Appendix H.

Crohns Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix H.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix I.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1. A copy of the questionnaire is located in Appendix K.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix N, Appendix T).

The subjects parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

If a subject is no longer taken care of by their parent or legal guardian, the WPAI-CD should not be completed (neither by the subject's parent or legal guardian nor by the subject himself/herself).

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x-ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by AbbVie Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr)/SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Week 408/ET visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s).

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix M for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subjects home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study drug

administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix P.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/-3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/-3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06-806).

5.3.2 Drug Concentration Measurements

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collected prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

5.3.2.1 Collection of Samples for Analysis

Collection of Samples for Adalimumab Analysis

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A minimum of 17 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

For subjects who have a flare and require switching to higher dose or change dose to ew dosing, up to 2 additional samples are planned to be collected per subject for adalimumab analysis.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A minimum of 17 blood samples are planned to be collected per subject for AAA analysis.

For subjects who have a flare and require switching to higher dose or change dose to ew dosing, up to 2 additional samples are planned to be collected per subject for AAA analysis.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a –20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

5.3.2.3 Disposition of Samples

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither AbbVie nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at AbbVie. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

5.3.5 Pharmacokinetic Variables

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subjects legal guardian requests withdrawal from the study.

- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 408/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subjects condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigators best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

AbbVie reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records

- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL or in vials containing adalimumab 40 mg/0.8mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score

(regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

The dose of adalimumab may be decreased to the next lower treatment level as applicable, at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes (used for 40 mg/0.8 mL or 20 mg/0.4 mL doses) and 40 mg/0.8 mL vials (used for 10 mg dose) will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott
Adalimumab	40 mg/0.8 mL (used for 10 mg dose) Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott

5.5.2.1 Packaging and Labeling

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4). Each kit will be labeled as required per country requirement. Labels must remain affixed to the kit.

Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.
Open-label Vials (used for 10 mg dose)	
Open-label kit cartons containing two vials of adalimumab 40 mg/0.8 mL.	

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes and vials are to be stored protected from light at 2° to 8°C/36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call-in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06-806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The dose of adalimumab may be decreased to the next lower treatment level as applicable at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix P).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes and vials will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes or vials dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes and vials will be inventoried and returned to an identified vendor for disposal as

designated by AbbVie. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix S. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes and vials will be inventoried by the site and verified by the CRA. The used syringes and vials will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit or vials boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal container to store expelled/used syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes and used vials have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohns disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 before Amendment 4 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD before Amendment 4. A model based on the JRA population was chosen because the body weight range would closely parallel that in a juvenile CD population. Escalation to weekly dosing would provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provides investigators with the option of dose de-escalation by reducing the dose or switching from ew to eow based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients will have the option to be switched

to this dose based on their body weight and clinical status at the discretion of the investigator.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe)

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

6.1.1 Definitions

6.1.1.1 Adverse Event

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to AbbVie within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subjects hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subjects usual activities.
Severe	The AE causes considerable interference with the subjects usual activities and may be incapacitating or life threatening.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

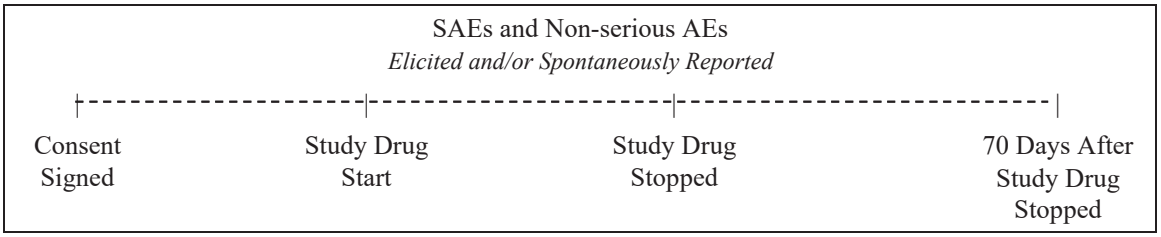
If an Investigators opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will notify AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by faxing or emailing the serious adverse event or nonserious event of malignancy in patients 30 years of age and younger forms to the Immunology Clinical Safety Team within 24 hours of being made aware of the adverse event.

To report a Serious Adverse Event (SAE):

AbbVie Safety Fax Number: [redacted]

Email: [redacted]

For SAE concerns, contact the Immunology Safety Team at:

[redacted]

For any subject safety concerns, contact the physician listed below:

Primary Study Designated Physician:

[redacted]

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: [redacted]

6.1.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohns disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product

Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following AbbVie representative:

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn

- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind Study M06-806).

8.1.2.2 Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subjects last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

Efficacy will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Race [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]
- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be provided to cross-classify and tabulate subjects value from baseline to final value by the presence of clinically significant laboratory results. Each subjects baseline value and final value will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.4.1 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

8.1.5 Interim Analysis

There will be multiple planned interim analyses. Details of the analyses will be described in the study SAPs.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigators Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix C.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study

and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institutions IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subjects parent/legal guardian. The original signed ICF and Assent Form will be placed in the subjects medical record. An entry must also be made in the subjects dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by AbbVie. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction

fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by AbbVie. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigators meeting will be held with AbbVie personnel, the Investigators and their study coordinators, the CROs project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigators meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at AbbVie.

All data hand entered in the database will be verified by a double-key entry procedure at AbbVie. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

Sites will provide AbbVie (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical

study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and AbbVie. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to AbbVie or their designee.

AbbVie may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to AbbVie a reasonable time

in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigators Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subjects last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigators Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title:	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
Protocol Date:	26 May 2015

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohns disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form

IRB	Institutional Review Board
ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N-telopeptide
OL	Open-Label
PCDAI	Pediatric Crohns Disease Activity Index
PK	Pharmacokinetics
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohns Disease

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Statistics
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, AbbVie has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigators agreement page for the study.
2. A signed and dated Form FDA 1572 certifying the investigators agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigators agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.
3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.
4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).
   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institutions General Assurance Number.
   - If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.
6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.
8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union.

Appendix D. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (AbbVie), summarizing the Investigators qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying AbbVie, except when necessary to protect the safety, rights, or welfare of subjects.
2. To personally conduct or supervise the described investigation(s).
3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.
4. To report to AbbVie adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
5. To read and understand the information in the Investigators Brochure, including the potential risks and side effects of the drug.
6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.
7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of AbbVie, the IEC/IRB

and/or the appropriate regulatory agency, and to retain all study-related documents until notification from AbbVie. The Investigator must notify AbbVie when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from AbbVie to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix E. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

April 2006 Website - www.cdc.gov/tb Page 1 of 2

Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR-6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix F. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Dosing syringes, as applicable

Appendix G. Pediatric Crohns Disease Activity Index (PCDAI)

		Score
1. Abdominal pain rating		
- None	= 0 p	
- Mild - Brief, does not interfere with activities	= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal	= 10 p	
2. Stools (per day)		
- 0–1 liquid stools, no blood	= 0 p	
- Up to 2 semi-formed with small blood, or 2–5 liquid	= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	= 10 p	
3. Patient Functioning, General Well-Being		
- No limitation of activities, well	= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par	= 5 p	
- Frequent limitation of activity, very poor	= 10 p	

LABORATORY		**Score**
4. HCT: Male and female ≤ 10 years: ≥ 33 = 0 p 28-32 = 2.5 p < 28 = 5 p	Male 11–14 years: ≥ 35 = 0 p 30-34 = 2.5 p < 30 = 5 p	
Female 11–19 years: ≥ 34= 0 p 29-33 = 2.5 p < 29 = 5 p	Male 15–19 years: ≥ 37= 0 p 32-36 = 2.5 p < 32 = 5 p	
5. ESR (mm/hr) < 20 = 0 p 20-50 = 2.5 p > 50 = 5 p		
6. Albumin (g/dL) ≥ 3.5 = 0 p 3.1-3.4 = 5 p ≤ 3.0 = 10 p		

EXAMINATION			**Score**
7. Weight	- Weight gain or voluntary weight stable/loss - Involuntary weight stable, weight loss 1–9% - Weight loss ≥ 10%	= 0 p = 5 p = 10 p	
8. Height	Height velocity ≥ -1SD Height velocity < -1SD, > -2SD Height velocity ≤ -2SD	= 0 p = 5 p = 10 p	
9. Abdomen	- No tenderness, no mass - Tenderness, or mass without tenderness - Tenderness, involuntary guarding, definite mass	= 0 p = 5 p = 10 p	
10. Perirectal disease	- None, asymptomatic tags - 1–2 indolent fistula, scant drainage, no tenderness - Active fistula, drainage, tenderness, or abscess	= 0 p = 5 p = 10 p	
11. Extra-intestinal Manifestations (Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*) - None - One - ≥ Two		= 0 p = 5 p = 10 p	
TOTAL SCORE	**Pediatric Crohns Disease Activity Index (PCDAI)**		

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohns disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohns disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 408: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48
- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216
- From Week 264 to Week 288, use height from Week 240
- From Week 288 to Week 312, use height from Week 264
- From Week 312 to Week 336, use height from Week 288
- From Week 336 to Week 360, use height from Week 312
- From Week 360 to Week 384, use height from Week 336
- From Week 384 to Week 408, use height from Week 360

The intent is to assess the normalcy vs. impairment of the subjects recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

   $$\frac{\text{Present height – Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:
   a. Velocity less than "Minus 2 SD" scores 10 points.
   b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.
   c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix I. Crohns Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	X	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: . (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix J. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. **Add item requested for each day.**	**Crohns Disease Activity Index Subject Diary Card**						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0 = none, 1 = mild, 2 = moderate, 3 = severe)							
Daily rating of general well being. (0 = well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)							

Subject Initials:_____ Subjects Signature:_____

Investigator or Designees Signature:_____

Appendix K. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohns disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I dont feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I dont think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I dont try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I dont feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix L. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix M. Day 70 Phone Call

Site Name/Number: _____

Subject Number: _____

Subject Initials: _____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.)

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Clinipace Worldwide at (949) 809-6506.

Appendix N. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohns disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times: _____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix O. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctors office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix P. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctors office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctors office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13 - Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263					

* Week 263 dose will only be taken if on every-week dosing schedule.

Week 264 - Week 288

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 264					
	Week 265					
	Week 266					
	Week 267					
	Week 268					
	Week 269					
	Week 270					
	Week 271					
	Week 272					
	Week 273					
	Week 274					
	Week 275					
	Week 276					
	Week 277					
	Week 278					
	Week 279					
	Week 280					
	Week 281					
	Week 282					
	Week 283					
	Week 284					
	Week 285					
	Week 286					
	Week 287					
	Week 288					

Week 289 - Week 312

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 289					
	Week 290					
	Week 291					
	Week 292					
	Week 293					
	Week 294					
	Week 295					
	Week 295					
	Week 296					
	Week 297					
	Week 298					
	Week 299					
	Week 300					
	Week 301					
	Week 302					
	Week 303					
	Week 304					
	Week 305					
	Week 306					
	Week 307					
	Week 308					
	Week 309					
	Week 310					
	Week 311					
	Week 312					

Week 313 - Week 335

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 313					
	Week 314					
	Week 315					
	Week 316					
	Week 317					
	Week 318					
	Week 319					
	Week 320					
	Week 321					
	Week 322					
	Week 323					
	Week 324					
	Week 325					
	Week 326					
	Week 327					
	Week 328					
	Week 329					
	Week 330					
	Week 331					
	Week 332					
	Week 333					
	Week 334					
	Week 335					

* Week 335 dose will only be taken if on every-week dosing schedule.

Week 336 - Week 360

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 336					
	Week 337					
	Week 338					
	Week 339					
	Week 340					
	Week 341					
	Week 342					
	Week 343					
	Week 344					
	Week 345					
	Week 346					
	Week 347					
	Week 348					
	Week 349					
	Week 350					
	Week 351					
	Week 352					
	Week 353					
	Week 354					
	Week 355					
	Week 356					
	Week 357					
	Week 358					
	Week 359					
	Week 360					

Week 361 - Week 384

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 361					
	Week 362					
	Week 363					
	Week 364					
	Week 365					
	Week 366					
	Week 367					
	Week 368					
	Week 369					
	Week 370					
	Week 371					
	Week 372					
	Week 373					
	Week 374					
	Week 375					
	Week 376					
	Week 377					
	Week 378					
	Week 379					
	Week 380					
	Week 381					
	Week 382					
	Week 383					
	Week 384					

Week 385 - Week 408

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 385					
	Week 386					
	Week 387					
	Week 388					
	Week 389					
	Week 390					
	Week 391					
	Week 392					
	Week 393					
	Week 394					
	Week 395					
	Week 396					
	Week 397					
	Week 398					
	Week 399					
	Week 400					
	Week 401					
	Week 402					
	Week 403					
	Week 404					
	Week 405					
	Week 406					
	Week 407					
	Week 408					

Appendix Q. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360 and 384) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

For 40 mg dose, one pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 20 mg dose, one pre-filled syringe will contain 0.4 mL of liquid. The total available dose is 0.4 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

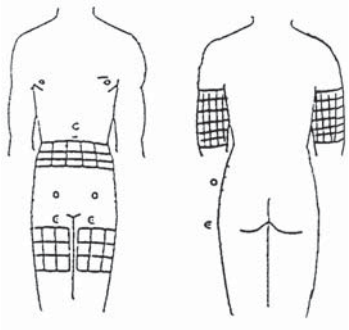
Remember to complete your dosing diary after each injection and to call the doctors office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

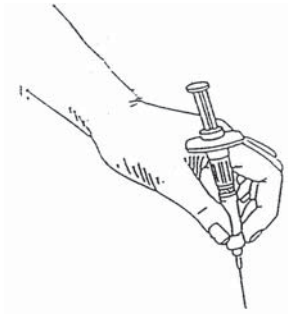
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



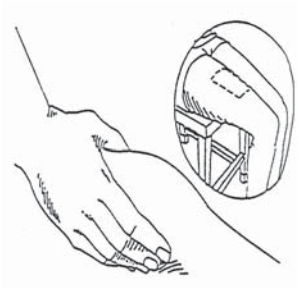
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

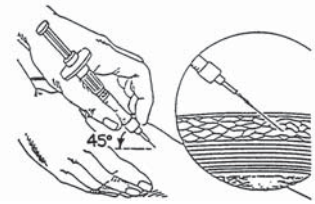


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

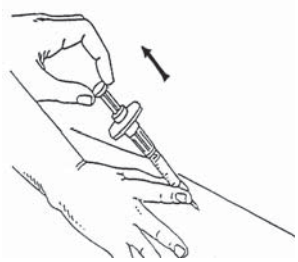
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

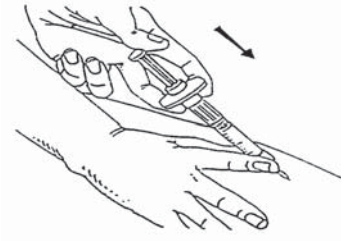


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



11. Remove needle while maintaining a 45-degree angle.

12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Self Injection Instructions

Subject Instructions

0.2 mL dose

Vials

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Vials**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360 and 384 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

The total dose is 0.2 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 10 mg dose, 0.2 mL of the solution is drawn from a vial containing adalimumab 40 mg/0.8 mL solution. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused vials to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused vials should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

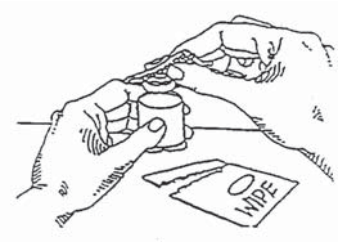
General Information **Vials**

- Vials will be labeled "adalimumab."
- Store all adalimumab vials in your refrigerator NOT in the freezer. Should the vials accidentally become frozen, call your study coordinator.
- 0.2 mL = 0.2 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW VIAL EVERY INJECTION DAY.** There will be medication left in the vial. **DO NOT RE-USE.**
- Save all study drugs. ***Vials (used and unused) must be returned to the study center at each visit.*** Used vials and syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

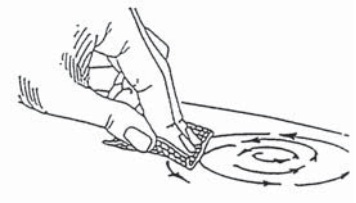
Injection Instructions **Vials**

Select a clean, well-lit, flat surface.

1. Wash your hands thoroughly with soap and warm water. It is important to keep your work surface as clean as possible.
2. Open carton.
3. Examine the carton and components in it to make sure they are complete.
    - One or two vials containing adalimumab
4. Remove the plastic cap from the vial.
5. Wipe the gray stopper with an alcohol swab and discard alcohol swab.



6. Place the vial upright on a hard, flat surface.
7. Choose an injection site on the upper thigh or abdomen.
8. Prepare the injection site by wiping it thoroughly with a second alcohol swab. Use a circular motion.



9. Remove the needle cover from the syringe. *(The needle is sterile, so be very careful not to touch the needle or allow it to touch any surface.)*

10. Draw the plunger on the syringe back.

11. With the vial sitting on a hard, flat surface, insert needle straight down through the center of the gray stopper. If the needle is correctly lined up, you should feel slight resistance and then a "pop" as the needle penetrates the center of the stopper. (*Be careful not to insert the needle at an angle as this may cause the needle to bend. If the needle is not correctly aligned, you will feel constant resistance as it penetrates the stopper and will not feel a "pop.")*

12. Push the plunger in forcing air into the vial.

13. With the needle still in place, turn the vial upside down. Keeping the vial at eye level, slowly pull the plunger back to draw the liquid into the syringe. This will cause the bubbles to rise to the top of the syringe. *(As the liquid level in the vial drops, you may have to withdraw the needle partially to keep the tip of the needle in the liquid.)* Only 0.2 mL of the vial will be drawn into the syringe.

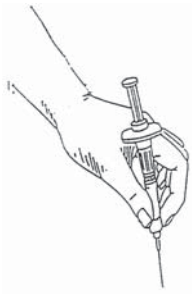
14. With the needle still in the vial, check the syringe for air bubbles. To remove any air bubbles, start by gently tapping the syringe.

15. Slowly press the plunger to push any bubbles out of the syringe and into the vial. *(If you accidentally push any liquid back into the vial, draw the liquid back into the syringe and check again for air bubbles. It's okay for a small amount of liquid to remain in the vial.)*

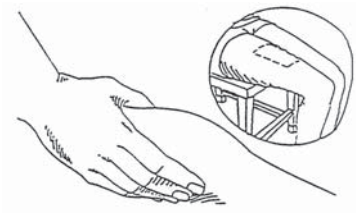
16. Withdraw the needle from the vial, being careful not to touch it to any surface.

Vials

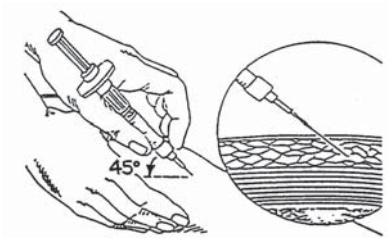
17. Take the syringe in one hand.



18. With your other hand, firmly pinch the skin around the cleaned injection site. *(Be careful not to touch the cleaned area.)*



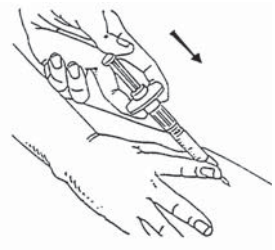
19. Hold the syringe at about a 45-degree angle to the skin and use a quick, short motion to push the needle into the skin.



20. Once the needle is in, release the skin.

Vials

21. While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. Only 0.2 mL of the vial will be injected.



22. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same 45-degree angle.

23. Dispose of both the needle and syringe in a puncture-resistant container, or sharps container, which will be provided.

24. You may want to press a cotton ball on the injection site for 10 seconds. If there is some slight bleeding, you may choose to apply a small bandage.

25. Return the vial into the original packaging.

26. Place the medication kit back into the refrigerator.

Vials

EACH TIME YOU RECEIVE AN INJECTION OF STUDY MEDICATION, REMEMBER TO RECORD THE INFORMATION ON YOUR DOSING SHEET.

GENERAL INFORMATION:

27. ROTATING INJECTION SITES IS RECOMMENDED. PLEASE DO NOT INJECT THE STUDY MEDICATION INTO A PRIOR SITE OF INJECTION.

28. Store all of your drug in the refrigerator. Should the vials become accidentally frozen or left out, call your study coordinator. DO NOT USE THESE VIALS.

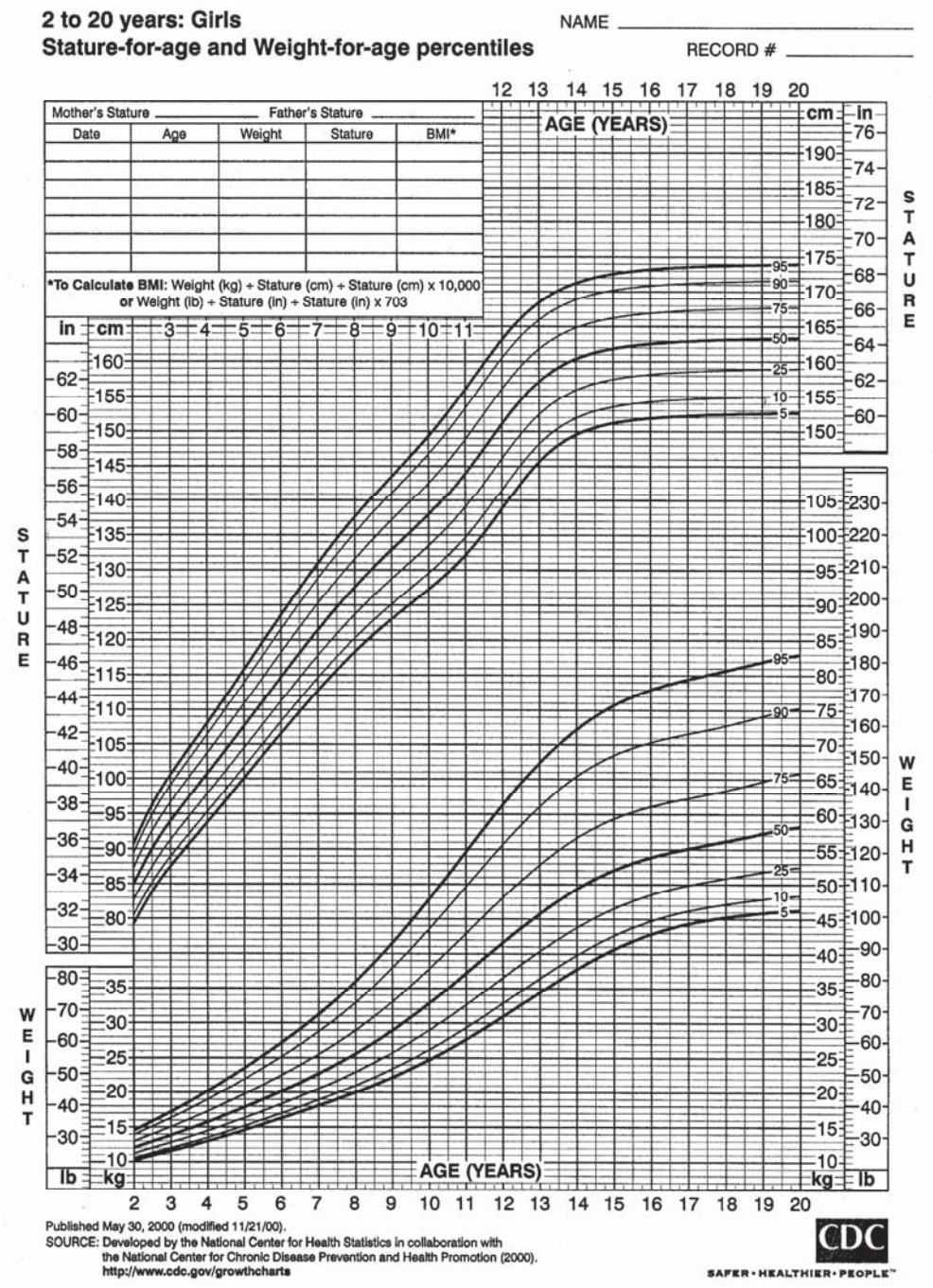
29. If you forget to take the drug or make a mistake with an injection, please call your study coordinator.

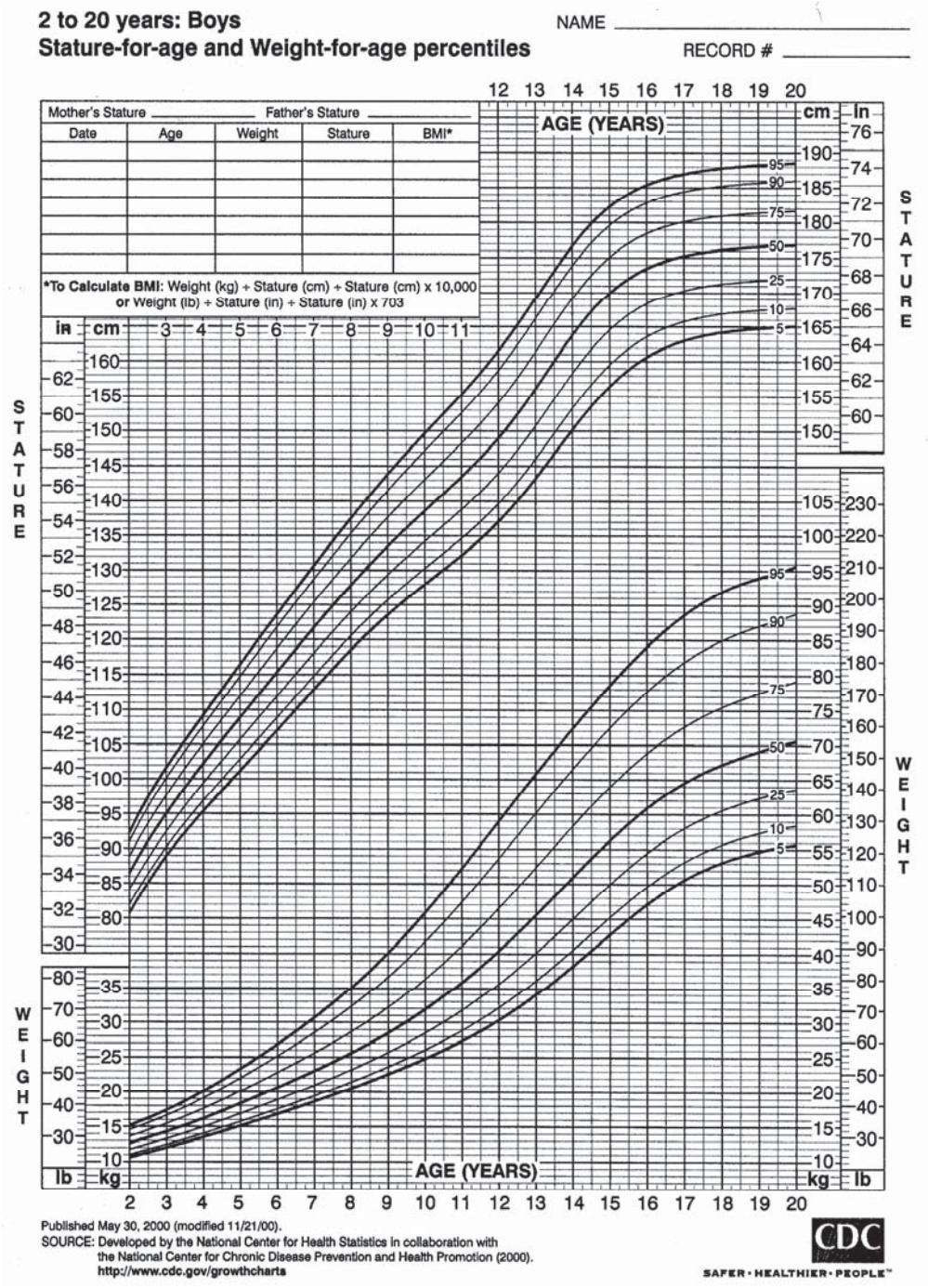
30. Please save all of your study medication, even if you skip a dose. Please bring all used and unused vials back to the physician at your next study visit.

31. There will be study medication remaining in the vials. DO NOT USE THE MEDICATION LEFT IN THE VIAL. Please return the vial along with the remaining study medication back to the physician at your next study visit.

32. Specific side effects to watch for: redness and swelling at the injection site. Please tell the study coordinator if you have any side effects from injecting the drug.

Appendix R. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER · HEALTHIER · PEOPLE™

Appendix S. Subject AbbVie Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix T. Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) – Caregiver

The following questions ask about the effect of your childs Crohns disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

---

2. During the past seven days, how many hours did you miss from work because of problems associated with your childs Crohns disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your childs Crohns disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS (*If "0," skip to question 6.*)

5. During the past seven days, how much did your childs Crohns disease affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your childs Crohns disease *affected your work only a little, choose a low number. Choose a high number if your childs* Crohns disease *affected your work a great deal.*

Consider only how much your childs Crohns disease affected your productivity while you were working.

My childs Crohns disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your childs Crohns Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your childs Crohns Disease affected your activities only a little, choose a low number. Choose a high number if your childs Crohns Disease affected your activities a great deal.

Consider only how much your childs Crohns disease affected your ability to do your regular daily activities, other than work at a job.

My childs Crohns disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:CD-Caregiver (US English)

Appendix U. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Emergency Contact:" previously read:

Emergency Contact:	Andreas Lazar, MD Associate Medical Director AbbVie Deutschland GmbH & Co. KG Knollstrasse Building 34, Room 214 67061 Ludwigshafen Germany	Office: Fax: Cell: Email:	49 621 589 2679 49 621 589 1288 49 160 9725 4782 andreas.lazar@abbvie.com

Has been changed to read:

Emergency Contact:	Andreas Lazar, MD Medical Director AbbVie Deutschland GmbH & Co. KG Knollstrasse Building 34, Room 214 67061 Ludwigshafen Germany	Office: Fax: Cell: Email:	49 621 589 2679 49 621 589 1288 49 160 9725 4782 andreas.lazar@abbvie.com

Section 5.1. Overall Study Design and Plan: Description
Eleventh paragraph, first sentence previously read:

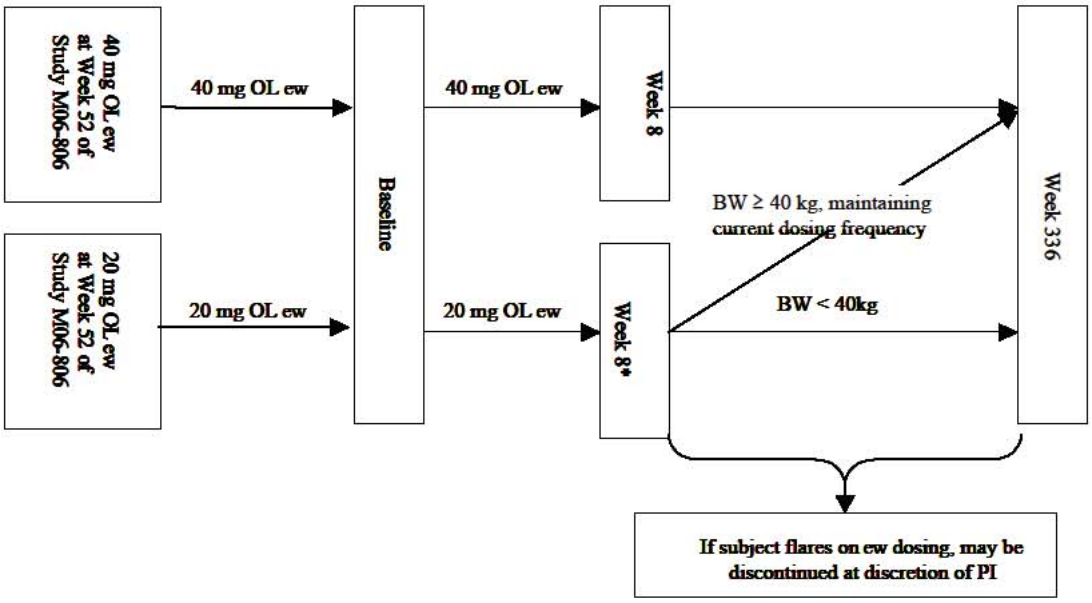
The duration of the study could last up to 336 weeks (approximately 6.5 years).

Has been changed to read:

The duration of the study could last up to 408 weeks (approximately 8 years).

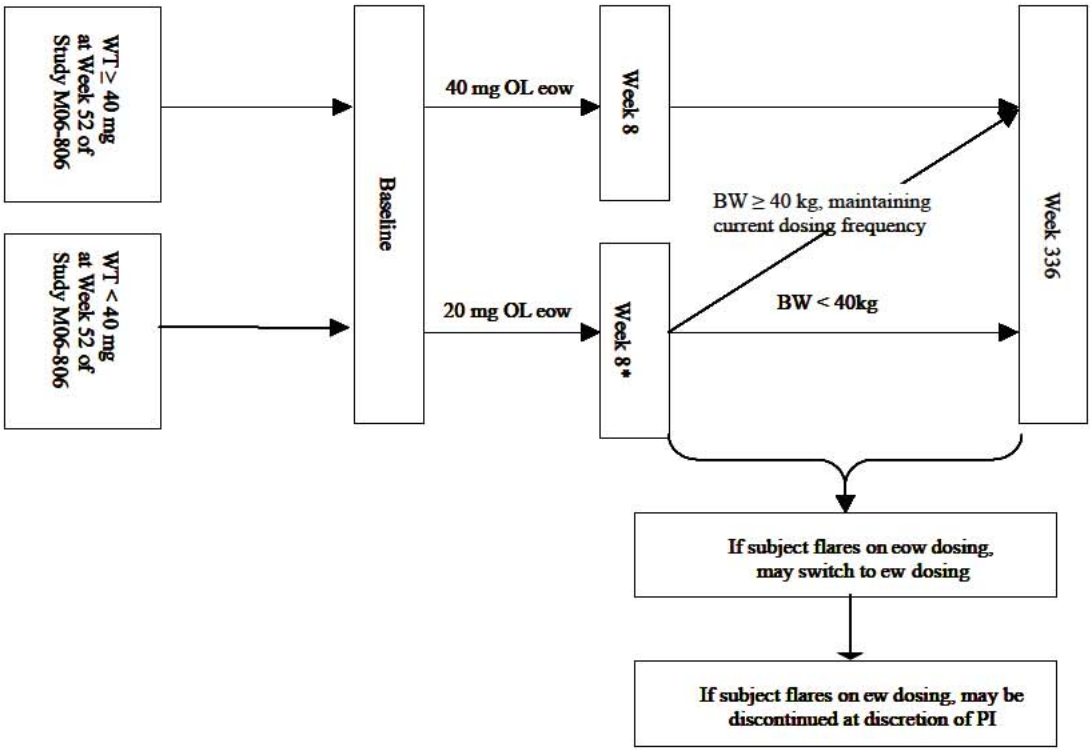
Figure 1. Study Schematic
Previously read:

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator.

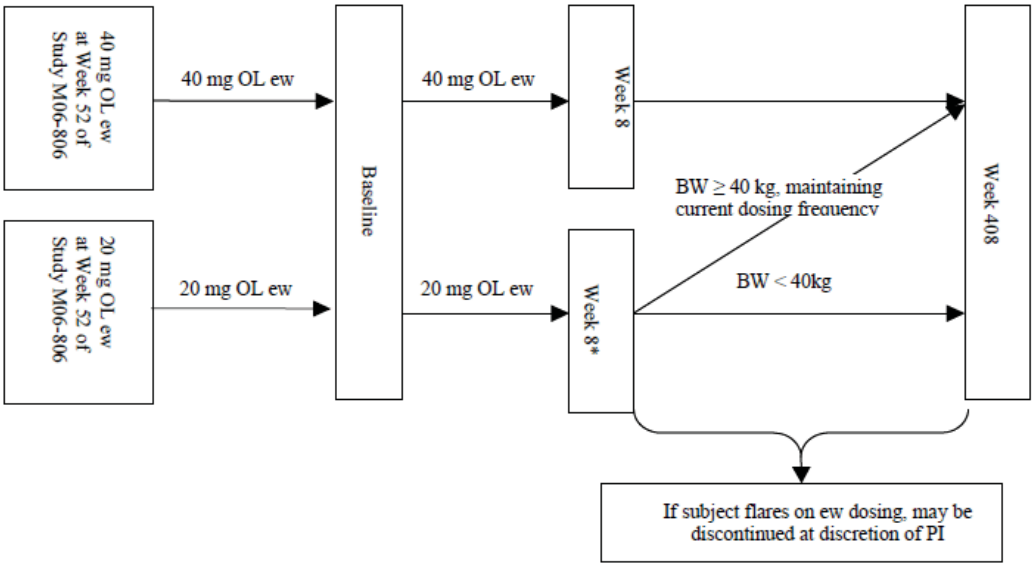
Subjects who enter M06807 Study from Double-Blind Dosing of M06-806 Study



***At or after Week 8 subjects on 20 mg OL dosing with an increasein BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator**

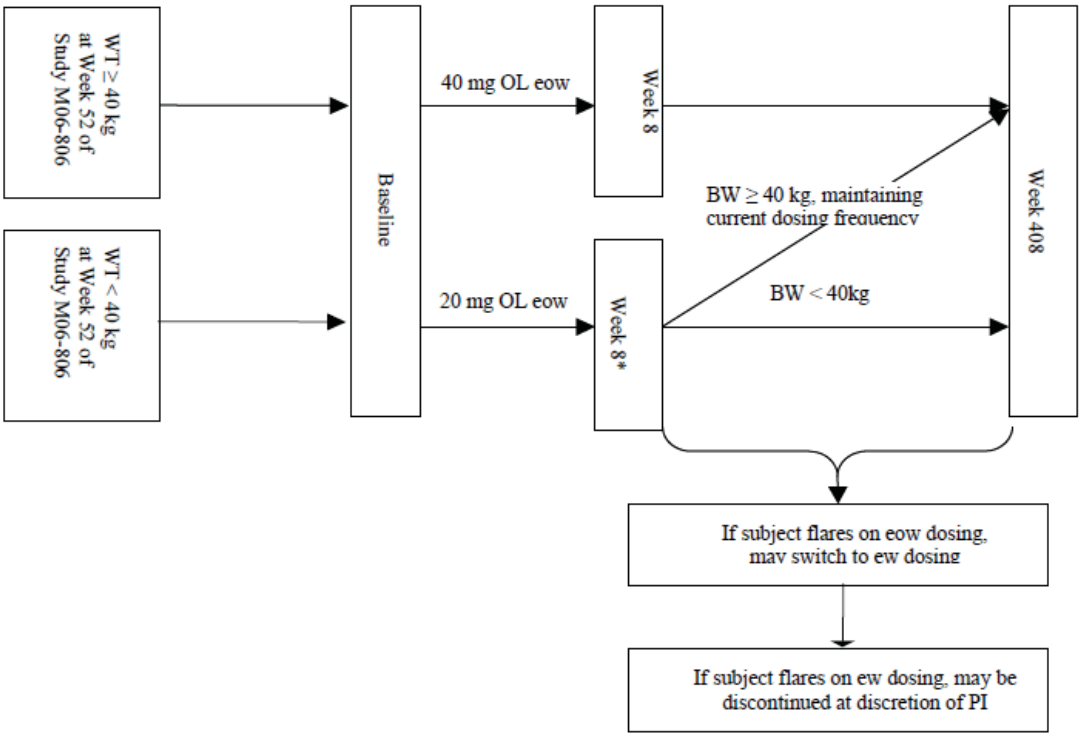
Has been changed to read:

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Table 1. Study Activities
Previously read:

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Inclusion/exclusion criteria	X									
Informed consent	X									
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X
TB testing (PPD or QuantiFERON-TB Gold)[m]							X			
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X	
ANA	X[a]			X						
Anti-dsDNA[f]	X[a]			X						
PCDAI	X[a]	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X	

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X			
Serum bone markers	X[a]				X		X		X	
PK Blood Sample[j]					X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Inclusion/exclusion criteria										
Informed consent										
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X	X	X		X		X		X	
Vital signs[c]	X	X	X		X		X		X	
Physical exam	X	X	X		X		X		X	
General LAB[d]	X	X	X		X		X		X	
TB testing (PPD or QuantiFERON-TB Gold)[m]	X				X				X	
Urinalysis[e]	X	X	X		X		X		X	
Erythrocyte sedimentation rate	X	X	X		X		X		X	
CRP		X			X		X		X	
ANA		X			X				X	
Anti-dsDNA[f]		X			X				X	
PCDAI	X	X	X		X		X		X	
CDAI[g]	X	X	X		X		X		X	
IMPACT III Questionnaire[h]		X	X		X		X		X	

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X	X	X		X		X		X	
X-ray for bone age[i]		X			X				X	
Serum bone markers[i]		X	X		X		X		X	
PK Blood Sample[j]	X		X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X		X		X		X	

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria													
Informed consent													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X	X	
TB testing (PPD or QuantiFERON-TB Gold)[m]			X				X				X		
Urinalysis[e]	X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X	X	
CRP	X				X		X		X		X		
ANA					X						X		
Anti-dsDNA[f]					X						X		
PCDAI	X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X	X	

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X		X		X		X		X		X	X	
X-ray for bone age[i]					X						X		
Serum bone markers[i]	X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X			X[l]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.

b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.

c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.

d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.

e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 - 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

f. If an ANA result is positive, anti-dsDNA will be performed automatically.

g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.

h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312 and 336/ET and unscheduled visits.

i. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.

j. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.

k. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).

l. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

m. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192, 240, 288 and 336.

Has been changed to read:

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Inclusion/exclusion criteria	X									
Informed consent	X									
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X
TB testing (PPD or QuantiFERON-TB Gold)[e]							X			
Urinalysis[f]	X[a]	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X	
ANA	X[a]			X						
Anti-dsDNA[g]	X[a]			X						
PCDAI	X[a]	X	X	X	X	X	X	X	X	X
CDAI[h]	X[a]	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[i]	X[a]			X	X		X		X	

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X
X-ray for bone age[j]	X[a]						X			
Serum bone markers	X[a]				X		X		X	
PK Blood Sample[k]					X		X		X	
Anti-adalimumab blood levels (AAA)[k]					X		X		X	
Adverse events[l]	X[a]	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Inclusion/exclusion criteria										
Informed consent										
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X	X	X		X		X		X	
Vital signs[c]	X	X	X		X		X		X	
Physical exam	X	X	X		X		X		X	
General LAB[d]	X	X	X		X		X		X	
TB testing (PPD or QuantiFERON-TB Gold)[e]	X				X				X	
Urinalysis[f]	X	X	X		X		X		X	
Erythrocyte sedimentation rate	X	X	X		X		X		X	
CRP		X			X		X		X	
ANA		X			X				X	
Anti-dsDNA[g]		X			X				X	
PCDAI	X	X	X		X		X		X	
CDAI[h]	X	X	X		X		X		X	
IMPACT III Questionnaire[i]		X	X		X		X		X	

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X	X	X		X		X		X	
X-ray for bone age[j]		X			X				X	
Serum bone markers[j]		X	X		X		X		X	
PK Blood Sample[k]	X		X		X		X		X	
Anti-adalimumab blood levels (AAA)[k]	X		X		X		X		X	
Adverse events[l]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X		X		X		X	

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336	Week 348 Call	Week 360
Inclusion/exclusion criteria													
Informed consent													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X		X		X		X		X		X		X
Vital signs[c]	X		X		X		X		X		X		X
Physical exam	X		X		X		X		X		X		X
General LAB[d]	X		X		X		X		X		X		X
TB testing (PPD or QuantiFERON-TB Gold)[e]			X				X				X		
Urinalysis[f]	X		X		X		X		X		X		X
Erythrocyte sedimentation rate	X		X		X		X		X		X		X
CRP	X				X		X		X		X		X
ANA					X								
Anti-dsDNA[g]					X								
PCDAI	X		X		X		X		X		X		X
CDAI[h]	X		X		X		X		X		X		X
IMPACT III Questionnaire[i]	X		X		X		X		X		X		X

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336	Week 348 Call	Week 360
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X		X		X		X		X		X		X
X-ray for bone age[j]					X				X				X
Serum bone markers[j]	X		X		X		X		X		X		X
PK Blood Sample[k]	X		X		X		X		X		X		X
Anti-adalimumab blood levels (AAA)[k]	X		X		X		X		X		X		X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X		X

Activity	Week 372 Call	Week 384	Week 396 Call	Week 408/ Early Term	Unsched Visit	70-Day Follow-Up Call
Inclusion/exclusion criteria						
Informed consent						
Previous and concomitant medications	X	X	X	X	X	
Urine pregnancy test[b]		X		X	X	
Vital signs[c]		X		X	X	
Physical exam		X		X	X	
General LAB[d]		X		X	X	
TB testing (PPD or QuantiFERON-TB Gold)[e]		X		X		
Urinalysis[f]		X		X	X	
Erythrocyte sedimentation rate		X		X	X	
CRP		X		X	X	
ANA				X		
Anti-dsDNA[g]				X		
PCDAI		X		X	X	
CDAI[h]		X		X	X	
IMPACT III Questionnaire[i]		X		X	X	
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	

Activity	Week 372 Call	Week 384	Week 396 Call	Week 408/ Early Term	Unsched Visit	70-Day Follow Up Call
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)		X		X	X	
X-ray for bone age[j]				X		
Serum bone markers[j]		X		X	X	
PK Blood Sample[k]		X		X	X	
Anti-adalimumab blood levels (AAA)[k]		X		X	X	
Adverse events[l]	X	X	X	X	X	X
Dispense study drug		X			X[m]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.

b. Performed on all females of child bearing potential – Urine pregnancy test at all study visits.

c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.

d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.

e. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192, 240, 288, 336, 384 and 408/ET. No annual TB test should be done at Week 408 or at ET if already done at Week 384 or later.

f. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 – 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

g. If an ANA result is positive, anti-dsDNA will be performed automatically.

h. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.

i. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408/ETC and unscheduled visits.

j. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.

k. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.

l. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).

m. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

Section 5.3.1.1 Study Procedures
First paragraph, last sentence previously read:

The site will call the subjects at Weeks 132, 156, 180, 204, 228, 252, 276, 300 and 324 in order to collect any safety information from the subject as illustrated in Table 1.

Has been changed to read:

The site will call the subjects at Weeks 132, 156, 180, 204, 228, 252, 276, 300, 324, 348, 372 and 396 in order to collect any safety information from the subject as illustrated in Table 1.

Section 5.3.1.1 Study Procedures
Subsection Previous and Concomitant Medications
First paragraph, first sentence previously read:

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 336/ET visit.

Has been changed to read:

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 408/ET visit.

Section 5.3.1.1 Study Procedures
Subsection TB Testing
Second paragraph previously read:

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, 240, 288 and 336.

Has been changed to read:

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, 240, 288, 336 and 384. TB testing should not be done at Week 408 or at the ET visit if a test was done at week 384 or later.

Section 5.3.1.1 Study Procedures
Subsection Adverse Events
First paragraph, first sentence previously read:

Adverse events will be assessed at every study visit from Baseline through the Week 336/ET visit.

Has been changed to read:

Adverse events will be assessed at every study visit from Baseline through the Week 408/ET visit.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Collection of Samples for Adalimumab Analysis
Second paragraph previously read:

A minimum of 14 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Has been changed to read:

A minimum of 17 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Collection of Samples for AAA Analysis
Second paragraph previously read:

A minimum of 14 blood samples are planned to be collected per subject for AAA analysis.

Has been changed to read:

A minimum of 17 blood samples are planned to be collected per subject for AAA analysis.

Section 5.4.1 Discontinuation of Individual Subjects
Second paragraph, first sentence previously read:

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 336/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

Has been changed to read:

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 408/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

Section 6.0 Complaints
Add: new section number and text

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe, pen).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

Section 6.0 through 6.6
Section number and title previously read:

6.0 Adverse Events

6.1 Definitions

6.1.1 Adverse Event

6.1.2 Serious Adverse Events

6.2 Adverse Event Severity

6.3 Relationship to Study Drug

6.4 Adverse Event Collection Period

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

6.6 Pregnancy

Has been changed to read:

6.0 Complaints

6.1 Medical Complaints

6.1.1 Definitions

6.1.1.1 Adverse Event

6.1.1.2 Serious Adverse Events

6.1.2 Adverse Event Severity

6.1.3 Relationship to Study Drug

6.1.4 Adverse Event Collection Period

6.1.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

6.1.6 Pregnancy

Section 6.5 Adverse Event Reporting
Previously read:

6.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will notify AbbVie within 24 hours of the physician becoming aware of the event by faxing the serious adverse event or non-serious event of malignancy in patients 30 years of age and younger forms to the Immunology Clinical Safety Team.

For all sites:

For questions regarding SAEs, please contact:

Has been changed to read:

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will notify AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by faxing or emailing the serious adverse event or nonserious event of malignancy in patients 30 years of age and younger forms to the Immunology Clinical Safety Team within 24 hours of being made aware of the adverse event.

To report a Serious Adverse Event (SAE):

AbbVie Safety Fax Number: [redacted]

Email: [redacted]

For SAE concerns, contact the Immunology Safety Team at:

[redacted]

For any subject safety concerns, contact the physician listed below:

Primary Study Designated Physician:

[redacted]

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: [redacted]

Section 6.2 Product Complaint
Add: new section and text, renumber subsequent sections

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s), if present (see below).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Section 7.0 Protocol Deviations
Contact information following first paragraph previously read:

Has been changed to read:

Section 8.1.3 Other Analyses
Third bullet previously read:

- Ethnicity [White, Non-white]

Has been changed to read:

- Race [White, Non-white]

Section 8.1.5 Interim Analysis
Previously read:

There will be one planned interim analysis. Details of the analysis will be described in the study SAP.

Has been changed to read:

There will be multiple planned interim analyses. Details of the analyses will be described in the study SAPs.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Statistics
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Statistics
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height
Subsection Physical Examination
Third paragraph previously read:

From Baseline to Week 336: use weight from previous visit

Has been changed to read:

From Baseline to Week 408: use weight from previous visit

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height
Subsection Physical Examination
Heading "Item 8. Height"
Add: new bullet 15, 16 and 17

- From Week 336 to Week 360, use height from Week 312
- From Week 360 to Week 384, use height from Week 336
- From Week 384 to Week 408, use height from Week 360

Appendix M. Day 70 Phone Call
Last paragraph, last sentence previously read:

Please fax this form to Paragon at [redacted]

Has been changed to read:

Please fax this form to Clinipace Worldwide at [redacted]

Appendix P. Subject Dosing Diary
Table: Week 241 - Week 263
Last row previously read:

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 263*					

Has been changed to read:

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 263					

Appendix P. Subject Dosing Diary
Table: Week 313 - Week 335
Row "Week 335*" previously read:

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 335*					

Has been changed to read:

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 335					

Appendix P. Subject Dosing Diary
Add table: Week 336 - Week 360

Week 336 - Week 360

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 336					
	Week 337					
	Week 338					
	Week 339					
	Week 340					
	Week 341					
	Week 342					
	Week 343					
	Week 344					
	Week 345					
	Week 346					
	Week 347					
	Week 348					
	Week 349					
	Week 350					
	Week 351					
	Week 352					
	Week 353					
	Week 354					
	Week 355					
	Week 356					
	Week 357					
	Week 358					

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 359					
	Week 360					

Appendix P. Subject Dosing Diary
Add table: Week 361 - Week 384

Week 361 - Week 384

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 361					
	Week 362					
	Week 363					
	Week 364					
	Week 365					
	Week 366					
	Week 367					
	Week 368					
	Week 369					
	Week 370					
	Week 371					
	Week 372					
	Week 373					
	Week 374					
	Week 375					
	Week 376					
	Week 377					
	Week 378					
	Week 379					
	Week 380					
	Week 381					
	Week 382					
	Week 383					
	Week 384					

Appendix P. Subject Dosing Diary
Add table: Week 385 - Week 408

Week 385 - Week 408

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 385					
	Week 386					
	Week 387					
	Week 388					
	Week 389					
	Week 390					
	Week 391					
	Week 392					
	Week 393					
	Week 394					
	Week 395					
	Week 396					
	Week 397					
	Week 398					
	Week 399					
	Week 400					
	Week 401					
	Week 402					
	Week 403					
	Week 404					
	Week 405					
	Week 406					
	Week 407					
	Week 408					

Appendix Q. Self Injection Instructions
Subsection Study Drug Dosing Schedule Open-Label (PFS)
Second paragraph, first sentence previously read:

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288 and 312) will be done during your visit, at the doctors office.

Has been changed to read:

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360 and 384) will be done during your visit, at the doctors office.

Appendix Q. Self Injection Instructions
Subsection Study Drug Dosing Schedule Vials
Second paragraph, first sentence previously read:

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288 and 312 will be done during your visit at the doctor's office.

Has been changed to read:

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360 and 384 will be done during your visit at the doctor's office.

Document Approval

Study M06807 - 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 Crohns Disease Who Have Demonstrated a Clinical Response in the M06-806 Study - Amendment 7 - EudraCT 2007-006494-90 - 26May2015

Version: 1.0 **Date:** 28-May-2015 01:49:42 PM **Company ID:** 05282015-00F9F680D59989-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	26-May-2015 05:38:09 PM	Approver
	26-May-2015 06:25:56 PM	Approver
	26-May-2015 06:40:03 PM	Author
	27-May-2015 07:23:14 P	Approver
	28-May-2015 01:49:40 PM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2, Amendment 1, Administrative Changes 3, 4, 5, 6 and 7 and Amendments 2, 3, 4, 5 and 6

AbbVie Number/ Investigational Product:	Adalimumab
Date:	12 April 2013
Development Phase:	3
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.
EudraCT Number:	2007-006494-90
Investigator:	Multicenter (Investigator information on file at AbbVie).
Sponsor:	European Union Countries: AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany Non European Union Countries: AbbVie 1 North Waukegan Road North Chicago, IL 60064
Emergency Contact:	[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is the following:

- Administrative Change 7 was incorporated.

  Rationale of Change: To reflect that AbbVie, the research-based pharmaceutical company, will now be the Sponsor of this study.

- Add subject visits through Week 336 throughout the protocol.

  Rationale of Change: Extension of this open-label study is necessary to allow for continued collection of long-term safety and efficacy information and provision for study to continue until local regulatory approval and reimbursement.

- Section 3.0, Section 5.2.3.1 and Section 6.5 were revised to include additional anti-TNF information per Humira standards, and provided background information about enhanced data collection to understand the risks of malignancy in subjects 30 and younger.

  Rationale: AbbVie is participating in an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in patients who are 30 years old or younger at the time of diagnosis.

- Section 5.2.3.2 Concomitant Therapy was revised to allow immunosuppressant to be started or restarted during the study. In addition, a sentence regarding the use of therapeutic enemas, suppositories and total parenteral nutrition was added to encourage the investigator to discuss with the Medical Monitor prior to use.

  Rationale of change: Due to medical and ethical considerations.

- Section 5.2.3.4 Prohibited Medication: The use of therapeutic enemas and suppositories was removed.

  Rationale of change: Due to medical and ethical considerations.

- Section 5.3.1.1 Study Procedures (Outcomes): A clarification on the completion procedure of the Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD): Caregiver was added.
- Section 5.3.2.1 Collection of samples for analysis: A clarification on collecting samples for subjects that require switching or change dose was added.
- Section 5.5.2.1 Packaging and Labeling was revised.
- Section 6.6 Pregnancy: The verbiage regarding the pregnancy registry was removed.

  Rationale of change: Registry is closed to Humira subjects, and is only enrolling in the comparator (non-Humira) arm.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix U.

2.0 Table of Contents

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3.0 Introduction

Crohns Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is heterogeneous

with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohns disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohns disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and 133 subjects continued in a 32-week double blind segment. Clinically significant

improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigators Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease. The subject population will consist of subjects who participated in and successfully completed the

M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigators discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigators discretion. For a detailed description of the study please see Section 5.0.

Safety Information

In 2008 FDA issued an early communication about an ongoing safety review of TNF blockers and the development of lymphoma and other cancers in children and adolescents.

As of the December 2009 FDA Pediatric advisory committee, it was noted that in general, adverse events seen in studies submitted for the JIA indication were similar to those in the adult population, both in type and frequency.

Due to the relatively rare occurrence of these cancers, the limited number of pediatric patients treated with TNF blockers, and the possible role of other immunosuppressive therapies used concomitantly with TNF blockers, the FDA was unable at that time to fully characterize the strength of the association between using TNF blockers and developing a malignancy. Product labeling for all anti-TNF agents now includes language regarding the risk of pediatric malignancies as requested by the FDA.

Furthermore, in November 2011 the FDA requested that all manufacturers of TNF inhibitors undertake a coordinated effort to better understand the risks for malignancies that develop in patients who are 30 years of age and younger at the time of diagnosis. Reporting requirements for these events can be found in Section 6.5 Adverse Event Reporting. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience with adalimumab can be found in the current Investigator's Brochure.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow

treatment. A disease flare is defined as an increase in the Pediatric Crohns Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI score obtained at the subjects previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohns treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohns specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 336 weeks (approximately 6.5 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohns Disease.
- All applicable local reimbursement procedures are completed.

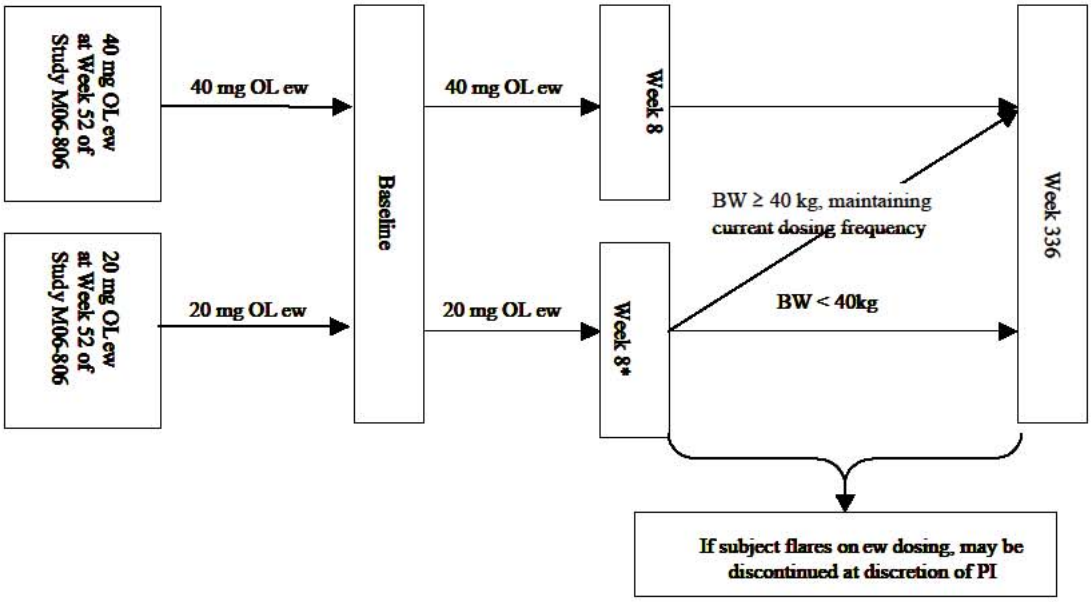
Sites will be notified once these criteria are met.

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

A schematic of the study design is shown in Figure 1 (prior to Amendment 4) and in Figure 2 (after Amendment 4).

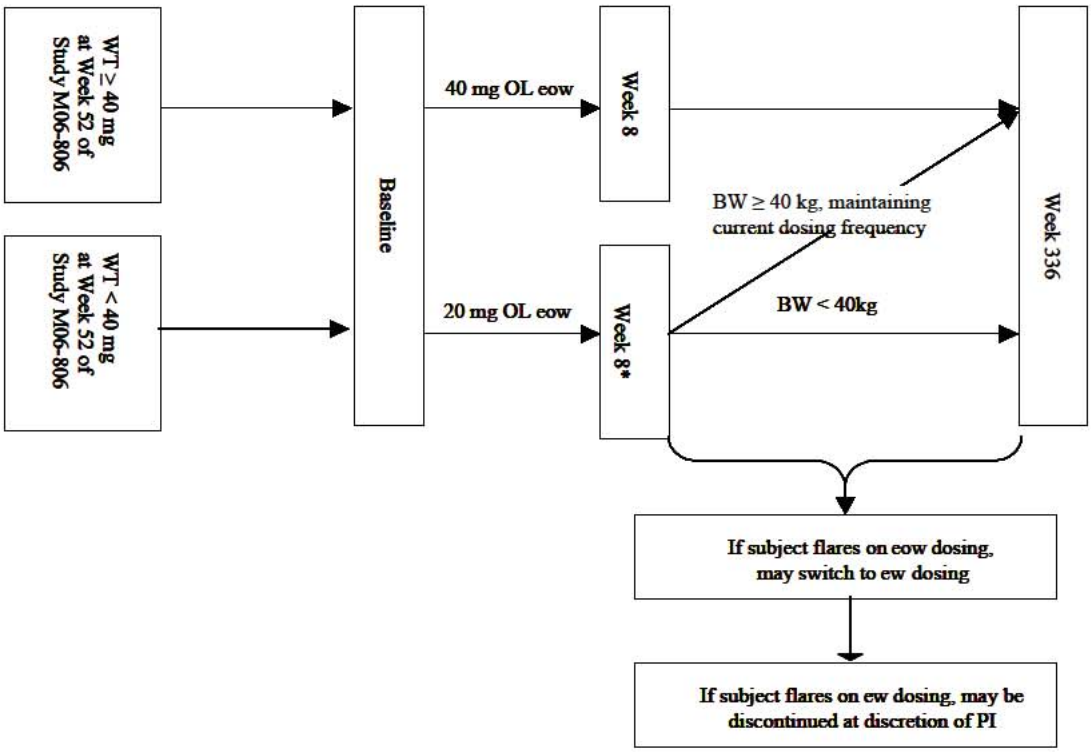
Figure 1. Study Schematic

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



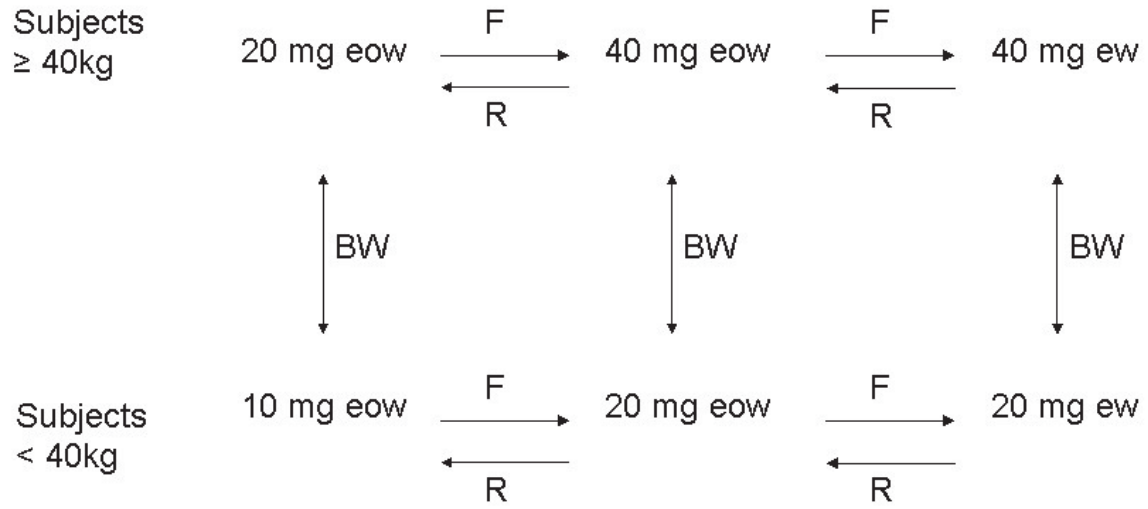
* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator.

Subjects who enter M06807 Study from Double-Blind Dosing of M06-806 Study



***At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator**

Figure 2. Dosing Schematic After Amendment 4



F: Subjects who have a disease flare may be switched to the next higher treatment level.

R: Subjects who responded to their current treatment may be switched to the next lower treatment level at the discretion of the investigator after discussion with the medical monitor. Response is defined as a) a ≥ 15 points decrease in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) a ≥ 15 points decrease in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate.

BW: Subjects with an increase in body weight to ≥ 40 kg may increase their dose to the next higher level at the discretion of the investigator after discussion with the medical monitor. Subjects with a decrease in body weight to < 40 kg may decrease their dose to the next lower level at the discretion of the investigator after discussion with the medical monitor.

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subjects parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subjects diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohns disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma-in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the AbbVie Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the AbbVie Medical Monitor identified in Section 7.0

In addition for patients age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate CRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate CRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate CRF pages.

5.2.3.2 Concomitant Therapy

Adjustments of Crohn's related concomitant treatments, including Crohn's related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohn's related antibiotics or Crohn's related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the AbbVie Medical Monitor. In addition, subjects may be able to initiate or reinitiate Crohn's related treatments, following eight (8) weeks of exposure to open-label adalimumab. Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and total parenteral nutrition (TPN) during the study should be discussed with and approved by the Medical Monitor prior to use.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg ≤ 10 mg	5 mg/week 2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), and any investigational agent are prohibited during the study (see Appendix L).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Inclusion/exclusion criteria	X									
Informed consent	X									
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X
TB testing (PPD or QuantiFERON-TB Gold)[m]							X			
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X	
ANA	X[a]			X						
Anti-dsDNA[f]	X[a]			X						
PCDAI	X[a]	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X	

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X			
Serum bone markers	X[a]				X		X		X	
PK Blood Sample[j]					X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Inclusion/exclusion criteria										
Informed consent										
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X	X	X		X		X		X	
Vital signs[c]	X	X	X		X		X		X	
Physical exam	X	X	X		X		X		X	
General LAB[d]	X	X	X		X		X		X	
TB testing (PPD or QuantiFERON-TB Gold)[m]	X				X				X	
Urinalysis[e]	X	X	X		X		X		X	
Erythrocyte sedimentation rate	X	X	X		X		X		X	
CRP		X			X		X		X	
ANA		X			X				X	
Anti-dsDNA[f]		X			X				X	
PCDAI	X	X	X		X		X		X	
CDAI[g]	X	X	X		X		X		X	
IMPACT III Questionnaire[h]		X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X	X	X		X		X		X	
X-ray for bone age[i]		X			X				X	
Serum bone markers[i]		X	X		X		X		X	
PK Blood Sample[j]	X		X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria													
Informed consent													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X	X	
TB testing (PPD or QuantiFERON-TB Gold)[m]			X				X				X		
Urinalysis[e]	X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X	X	
CRP	X				X		X		X		X		
ANA					X						X		
Anti-dsDNA[f]					X						X		
PCDAI	X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X		X		X		X		X		X	X	
X-ray for bone age[i]					X						X		
Serum bone markers[i]	X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X			X[l]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.

b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.

c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.

d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.

Table 1. Study Activities (Continued)

e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 - 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

f. If an ANA result is positive, anti-dsDNA will be performed automatically.

g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.

h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312 and 336/ET and unscheduled visits.

i. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.

j. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.

k. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).

l. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

m. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192, 240, 288 and 336.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228, 252, 276, 300 and 324 in order to collect any safety information from the subject as illustrated in Table 1.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institutions IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of

legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 336/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subjects casebook from the previous study (M06-806). They will not be required to be captured in the subjects casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subjects M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix O) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

TB Testing

For subjects with a negative test at Screening visit from parent study (Study M06-806), an annual PPD or QuantiFERON-TB Gold re-test will be required. If one of the annual tests

has a positive test result, the matter should be discussed with the medical monitor prior to starting any prophylaxis.

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, 240, 288 and 336.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case must be discussed with the AbbVie Medical Monitor.

For the PPD test:

- The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The absence of induration should be recorded, as "0 mm," not "negative."
- If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.
- If QuantiFERON®-TB Gold (or equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or equivalent) result is indeterminate, this should be considered a positive test result and the case must be discussed with the AbbVie Medical Monitor.

In the event both a PPD test and QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test.

Newly initiated prophylactic treatment should be captured in the source documents and on the concomitant medications page in the CRF. Prior therapy should be captured in the appropriate medical history CRF.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of the PPD skin test and the CXR and has to give his/her opinion about the eligibility of each subject to continue in the study. This opinion must be documented in writing in the subject's source documents.

All subjects with a positive PPD need to be approved for continuation in the trial by both the Czech pulmonologist and the AbbVie Medical Monitor and all such subjects need to receive prophylaxis for latent TB. Under no circumstances can a subject with a positive PPD result and no prior history of treatment for active or latent TB be allowed to continue in this trial.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be

obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 - 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the sites local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured as indicated in Table 1. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5 - 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohns Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix G. Instructions for completing the PCDAI score is located in Appendix H.

Crohns Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix H.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix I.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1. A copy of the questionnaire is located in Appendix K.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix N, Appendix T).

The subjects parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

If a subject is no longer taken care of by their parent or legal guardian, the WPAI-CD should not be completed (neither by the subject's parent or legal guardian nor by the subject himself/herself).

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x-ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by AbbVie Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr)/SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Week 336/ET visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s).

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix M for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subjects home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study drug

administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix P.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/-3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/-3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06-806).

5.3.2 Drug Concentration Measurements

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collected prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

5.3.2.1 Collection of Samples for Analysis

Collection of Samples for Adalimumab Analysis

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A minimum of 14 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

For subjects who have a flare and require switching to higher dose or change dose to ew dosing, up to 2 additional samples are planned to be collected per subject for adalimumab analysis.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A minimum of 14 blood samples are planned to be collected per subject for AAA analysis.

For subjects who have a flare and require switching to higher dose or change dose to ew dosing, up to 2 additional samples are planned to be collected per subject for AAA analysis.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a –20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

5.3.2.3 Disposition of Samples

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither AbbVie nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at AbbVie. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

5.3.5 Pharmacokinetic Variables

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.

- The Investigator believes it is in the best interest of the subject.
- The subject or subjects legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 336/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subjects condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigators best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

AbbVie reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL or in vials containing adalimumab 40 mg/0.8mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

The dose of adalimumab may be decreased to the next lower treatment level as applicable, at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes (used for 40 mg/0.8 mL or 20 mg/0.4 mL doses) and 40 mg/0.8 mL vials (used for 10 mg dose) will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott
Adalimumab	40 mg/0.8 mL (used for 10 mg dose) Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie/Abbott

5.5.2.1 Packaging and Labeling

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4). Each kit will be labeled as required per country requirement. Labels must remain affixed to the kit.

Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.
Open-label Vials (used for 10 mg dose)	
Open-label kit cartons containing two vials of adalimumab 40 mg/0.8 mL.	

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes and vials are to be stored protected from light at 2° to 8°C/36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until AbbVie GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call-in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06-806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The dose of adalimumab may be decreased to the next lower treatment level as applicable at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will

receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix P).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes and vials will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes or vials dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes and vials will be inventoried and returned to an identified vendor for disposal as designated by AbbVie. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix S. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes and vials will be inventoried by the site and verified by the CRA. The used syringes and vials will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit or vials boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal container to store expelled/used syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes and used vials have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohns disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 before Amendment 4 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD before Amendment 4. A model based on the JRA population was chosen because the body weight range would closely parallel that in a

juvenile CD population. Escalation to weekly dosing would provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provides investigators with the option of dose de-escalation by reducing the dose or switching from ew to eow based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients will have the option to be switched to this dose based on their body weight and clinical status at the discretion of the investigator.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to AbbVie within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subjects hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subjects usual activities.
Severe	The AE causes considerable interference with the subjects usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

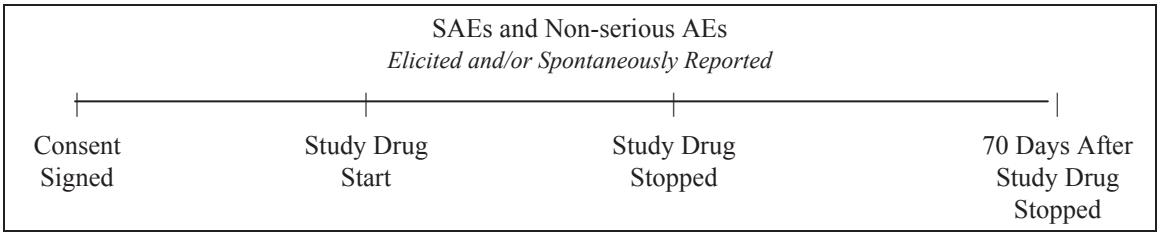
If an Investigators opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will notify AbbVie within 24 hours of the physician becoming aware of the event by faxing the serious adverse event or non-serious event of malignancy in patients 30 years of age and younger forms to the Immunology Clinical Safety Team.

For all sites:

[redacted]

For questions regarding SAEs, please contact:

[redacted]

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohns disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following AbbVie representative:

[redacted]

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807.

The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind Study M06-806).

8.1.2.2 Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subjects last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

Efficacy will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]

- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be provided to cross-classify and tabulate subjects value from baseline to final value by the presence of clinically significant laboratory results. Each subjects baseline value and final value will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.4.1 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

8.1.5 Interim Analysis

There will be one planned interim analysis. Details of the analysis will be described in the study SAP.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigators Brochure, the informed consent and all other forms of

subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix C.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institutions IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subjects parent/legal guardian. The original signed ICF and Assent Form will be placed in the subjects medical record. An entry must also be made in the subjects dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by AbbVie. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by AbbVie. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigators meeting will be held with AbbVie personnel, the Investigators and their study coordinators, the CROs project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigators meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at AbbVie.

All data hand entered in the database will be verified by a double-key entry procedure at AbbVie. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

Sites will provide AbbVie (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and AbbVie. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to AbbVie or their designee.

AbbVie may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to AbbVie a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigators Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subjects last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigators Agreement

1. I have received and reviewed the Investigator Brochure for Humira.

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title:	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
Protocol Date:	12 April 2013

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohns disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form

IRB	Institutional Review Board
ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N-telopeptide
OL	Open-Label
PCDAI	Pediatric Crohns Disease Activity Index
PK	Pharmacokinetics
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohns Disease

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Statistics
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, AbbVie has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigators agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigators agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigators agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).

- A dated list containing the names and affiliations of the members of the IEC/IRB, or the institutions General Assurance Number.
- If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union.

Appendix D. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (AbbVie), summarizing the Investigators qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying AbbVie, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to AbbVie adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigators Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of AbbVie, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from AbbVie. The Investigator must notify AbbVie when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from AbbVie to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix E. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

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Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix F. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Dosing syringes, as applicable

Appendix G. Pediatric Crohns Disease Activity Index (PCDAI)

						Score
1. Abdominal pain rating						
- None					= 0 p	
- Mild - Brief, does not interfere with activities					= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal					= 10 p	
2. Stools (per day)						
- 0–1 liquid stools, no blood					= 0 p	
- Up to 2 semi-formed with small blood, or 2–5 liquid					= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea					= 10 p	
3. Patient Functioning, General Well-Being						
- No limitation of activities, well					= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par					= 5 p	
- Frequent limitation of activity, very poor					= 10 p	
LABORATORY						**Score**
4. HCT: Male and female ≤ 10 years:	≥ 33	= 0 p	Male 11–14 years:	≥ 35	= 0 p	
	28-32	= 2.5 p		30-34	= 2.5 p	
	< 28	= 5 p		< 30	= 5 p	
Female 11–19 years:	≥ 34	= 0 p	Male 15–19 years:	≥ 37	= 0 p	
	29-33	= 2.5 p		32-36	= 2.5 p	
	< 29	= 5 p		< 32	= 5 p	
5. ESR (mm/hr)	< 20	= 0 p				
	20-50	= 2.5 p				
	> 50	= 5 p				
6. Albumin (g/dL)	≥ 3.5	= 0 p				
	3.1-3.4	= 5 p				
	≤ 3.0	= 10 p				

EXAMINATION			Score
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥ 10%	= 10 p	
8. Height			
	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations			
(Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)		= 0 p	
- None		= 5 p	
- One		= 10 p	
- ≥ Two			
TOTAL SCORE	**Pediatric Crohns Disease Activity Index (PCDAI)**		

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohns disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohns disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 336: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48
- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216
- From Week 264 to Week 288, use height from Week 240
- From Week 288 to Week 312, use height from Week 264
- From Week 312 to Week 336, use height from Week 288

The intent is to assess the normalcy vs. impairment of the subjects recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

   $$\frac{\text{Present height – Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

   a. Velocity less than "Minus 2 SD" scores 10 points.

   b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

   c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix I. Crohns Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	__+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	X	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix J. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. **Add item requested for each day.**	**Crohns Disease Activity Index Subject Diary Card**						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0 = none, 1 = mild, 2 = moderate, 3 = severe)							
Daily rating of general well being. (0 = well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)							

Subject Initials:_____ Subjects Signature:_____

Investigator or Designees Signature:_____

Appendix K. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohns disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I dont feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I dont think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I dont try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I dont feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix L. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix M. Day 70 Phone Call

Site Name/Number: _____

Subject Number: _____

Subject Initials: _____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted]

Appendix N. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohns disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times: _____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix O. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctors office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix P. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctors office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctors office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13 - Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263*					

* Week 263 dose will only be taken if on every-week dosing schedule.

Week 264 - Week 288

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 264					
	Week 265					
	Week 266					
	Week 267					
	Week 268					
	Week 269					
	Week 270					
	Week 271					
	Week 272					
	Week 273					
	Week 274					
	Week 275					
	Week 276					
	Week 277					
	Week 278					
	Week 279					
	Week 280					
	Week 281					
	Week 282					
	Week 283					
	Week 284					
	Week 285					
	Week 286					
	Week 287					
	Week 288					

Week 289 - Week 312

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 289					
	Week 290					
	Week 291					
	Week 292					
	Week 293					
	Week 294					
	Week 295					
	Week 295					
	Week 296					
	Week 297					
	Week 298					
	Week 299					
	Week 300					
	Week 301					
	Week 302					
	Week 303					
	Week 304					
	Week 305					
	Week 306					
	Week 307					
	Week 308					
	Week 309					
	Week 310					
	Week 311					
	Week 312					

Week 313 - Week 335

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 313					
	Week 314					
	Week 315					
	Week 316					
	Week 317					
	Week 318					
	Week 319					
	Week 320					
	Week 321					
	Week 322					
	Week 323					
	Week 324					
	Week 325					
	Week 326					
	Week 327					
	Week 328					
	Week 329					
	Week 330					
	Week 331					
	Week 332					
	Week 333					
	Week 334					
	Week 335*					

* Week 335 dose will only be taken if on every-week dosing schedule.

Appendix Q. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288 and 312) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

For 40 mg dose, one pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 20 mg dose, one pre-filled syringe will contain 0.4 mL of liquid. The total available dose is 0.4 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

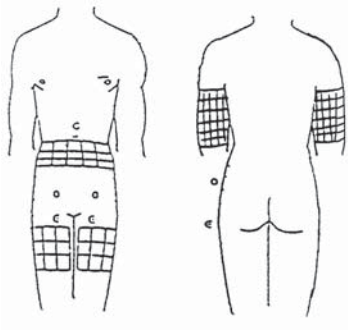
Remember to complete your dosing diary after each injection and to call the doctors office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

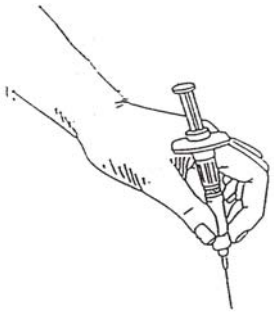
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



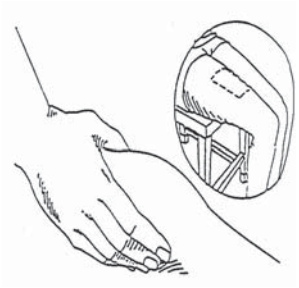
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

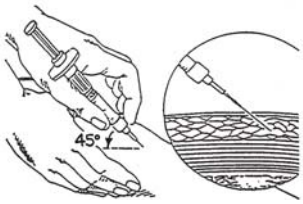


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

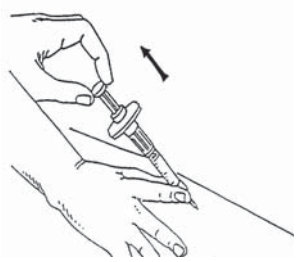
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

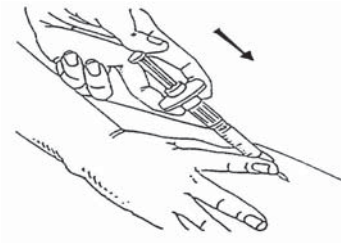


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



11. Remove needle while maintaining a 45-degree angle.

12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Self Injection Instructions

Subject Instructions

0.2 mL dose

Vials

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Vials**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288 and 312 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

The total dose is 0.2 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 10 mg dose, 0.2 mL of the solution is drawn from a vial containing adalimumab 40 mg/0.8 mL solution. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused vials to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused vials should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information **Vials**

- Vials will be labeled "adalimumab."
- Store all adalimumab vials in your refrigerator NOT in the freezer. Should the vials accidentally become frozen, call your study coordinator.
- 0.2 mL = 0.2 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW VIAL EVERY INJECTION DAY.** There will be medication left in the vial. **DO NOT RE-USE.**
- Save all study drugs. ***Vials (used and unused) must be returned to the study center at each visit.*** Used vials and syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

Injection Instructions **Vials**

Select a clean, well-lit, flat surface.

1. Wash your hands thoroughly with soap and warm water. It is important to keep your work surface as clean as possible.

2. Open carton.

3. Examine the carton and components in it to make sure they are complete.

   - One or two vials containing adalimumab

4. Remove the plastic cap from the vial.

5. Wipe the gray stopper with an alcohol swab and discard alcohol swab.

6. Place the vial upright on a hard, flat surface.

7. Choose an injection site on the upper thigh or abdomen.

8. Prepare the injection site by wiping it thoroughly with a second alcohol swab. Use a circular motion.

9. Remove the needle cover from the syringe. *(The needle is sterile, so be very careful not to touch the needle or allow it to touch any surface.)*

10. Draw the plunger on the syringe back.

11. With the vial sitting on a hard, flat surface, insert needle straight down through the center of the gray stopper. If the needle is correctly lined up, you should feel slight resistance and then a "pop" as the needle penetrates the center of the stopper. (*Be careful not to insert the needle at an angle as this may cause the needle to bend. If the needle is not correctly aligned, you will feel constant resistance as it penetrates the stopper and will not feel a "pop.")*

12. Push the plunger in forcing air into the vial.

13. With the needle still in place, turn the vial upside down. Keeping the vial at eye level, slowly pull the plunger back to draw the liquid into the syringe. This will cause the bubbles to rise to the top of the syringe. *(As the liquid level in the vial drops, you may have to withdraw the needle partially to keep the tip of the needle in the liquid.)* Only 0.2 mL of the vial will be drawn into the syringe.

14. With the needle still in the vial, check the syringe for air bubbles. To remove any air bubbles, start by gently tapping the syringe.

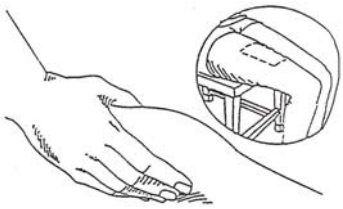
15. Slowly press the plunger to push any bubbles out of the syringe and into the vial. *(If you accidentally push any liquid back into the vial, draw the liquid back into the syringe and check again for air bubbles. It's okay for a small amount of liquid to remain in the vial.)*

16. Withdraw the needle from the vial, being careful not to touch it to any surface.

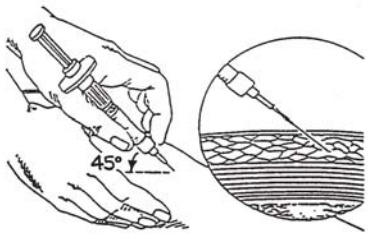
Vials

17. Take the syringe in one hand.

18. With your other hand, firmly pinch the skin around the cleaned injection site. *(Be careful not to touch the cleaned area.)*



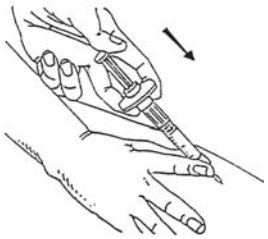
19. Hold the syringe at about a 45-degree angle to the skin and use a quick, short motion to push the needle into the skin.



20. Once the needle is in, release the skin.

Vials

21. While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. Only 0.2 mL of the vial will be injected.



22. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same 45-degree angle.

23. Dispose of both the needle and syringe in a puncture-resistant container, or sharps container, which will be provided.

24. You may want to press a cotton ball on the injection site for 10 seconds. If there is some slight bleeding, you may choose to apply a small bandage.

25. Return the vial into the original packaging.

26. Place the medication kit back into the refrigerator.

Vials

EACH TIME YOU RECEIVE AN INJECTION OF STUDY MEDICATION, REMEMBER TO RECORD THE INFORMATION ON YOUR DOSING SHEET.

GENERAL INFORMATION:

27. ROTATING INJECTION SITES IS RECOMMENDED. PLEASE DO NOT INJECT THE STUDY MEDICATION INTO A PRIOR SITE OF INJECTION.

28. Store all of your drug in the refrigerator. Should the vials become accidentally frozen or left out, call your study coordinator. DO NOT USE THESE VIALS.

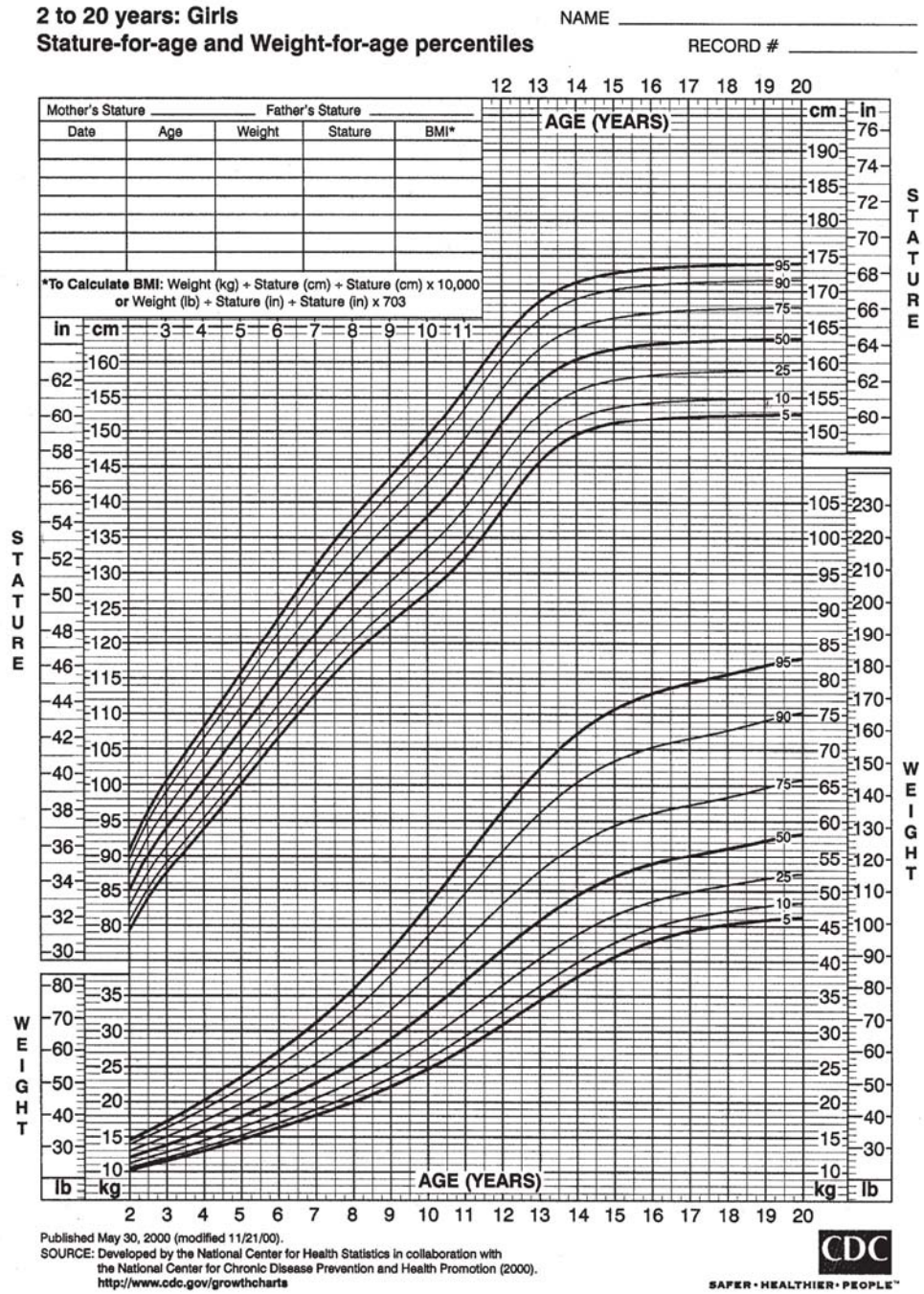
29. If you forget to take the drug or make a mistake with an injection, please call your study coordinator.

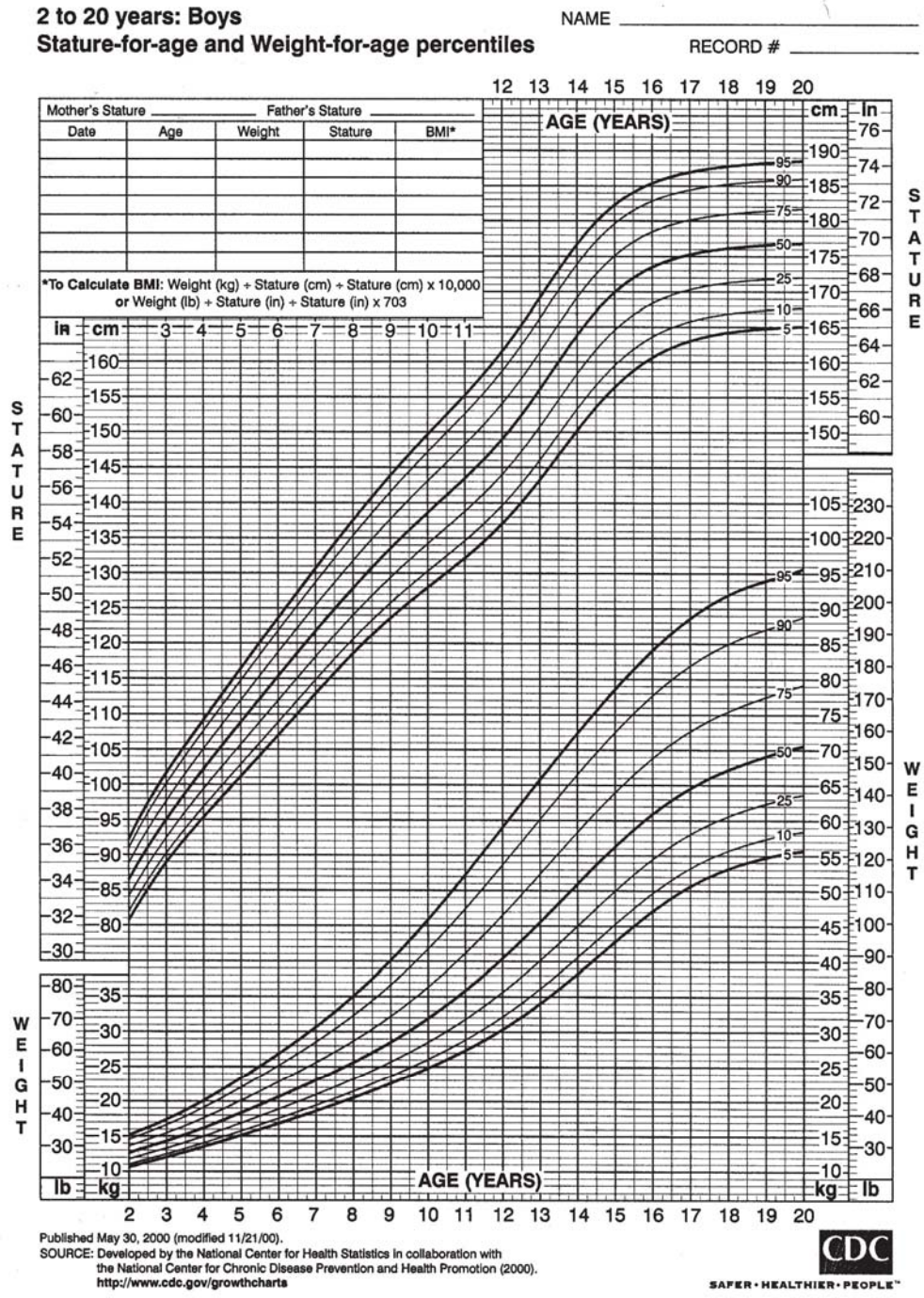
30. Please save all of your study medication, even if you skip a dose. Please bring all used and unused vials back to the physician at your next study visit.

31. There will be study medication remaining in the vials. DO NOT USE THE MEDICATION LEFT IN THE VIAL. Please return the vial along with the remaining study medication back to the physician at your next study visit.

32. Specific side effects to watch for: redness and swelling at the injection site. Please tell the study coordinator if you have any side effects from injecting the drug.

Appendix R. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER • HEALTHIER • PEOPLE™

Appendix S. Subject AbbVie Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix T. Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) – Caregiver

The following questions ask about the effect of your childs Crohns disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

---

2. During the past seven days, how many hours did you miss from work because of problems associated with your childs Crohns disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your childs Crohns disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS (*If "0," skip to question 6.*)

5. During the past seven days, how much did your childs Crohns disease affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your childs Crohns disease *affected your work only a little, choose a low number. Choose a high number if your childs* Crohns disease *affected your work a great deal.*

Consider only how much your childs Crohns disease affected your productivity while you were working.

My childs Crohns disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your childs Crohns Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your childs Crohns Disease affected your activities only a little, choose a low number. Choose a high number if your childs Crohns Disease affected your activities a great deal.

Consider only how much your childs Crohns disease affected your ability to do your regular daily activities, other than work at a job.

My childs Crohns disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix U. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Emergency Contact:" previously read:

Emergency Contact: [redacted]

Has been changed to read:

Emergency Contact: [redacted]

Section 3.0 Introduction
Add: Safety Information

Safety Information

In 2008 FDA issued an early communication about an ongoing safety review of TNF blockers and the development of lymphoma and other cancers in children and adolescents.

As of the December 2009 FDA Pediatric advisory committee, it was noted that in general, adverse events seen in studies submitted for the JIA indication were similar to those in the adult population, both in type and frequency.

Due to the relatively rare occurrence of these cancers, the limited number of pediatric patients treated with TNF blockers, and the possible role of other immunosuppressive therapies used concomitantly with TNF blockers, the FDA was unable at that time to fully characterize the strength of the association between using TNF blockers and developing a malignancy. Product labeling for all anti-TNF agents now includes language regarding the risk of pediatric malignancies as requested by the FDA.

Furthermore, in November 2011 the FDA requested that all manufacturers of TNF inhibitors undertake a coordinated effort to better understand the risks for malignancies that develop in patients who are 30 years of age and younger at the time of diagnosis. Reporting requirements for these events can be found in Section 6.5 Adverse Event Reporting. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience with adalimumab can be found in the current Investigator's Brochure.

Section 5.1 Overall Study Design and Plan: Description
Eleventh paragraph, first sentence previously read:

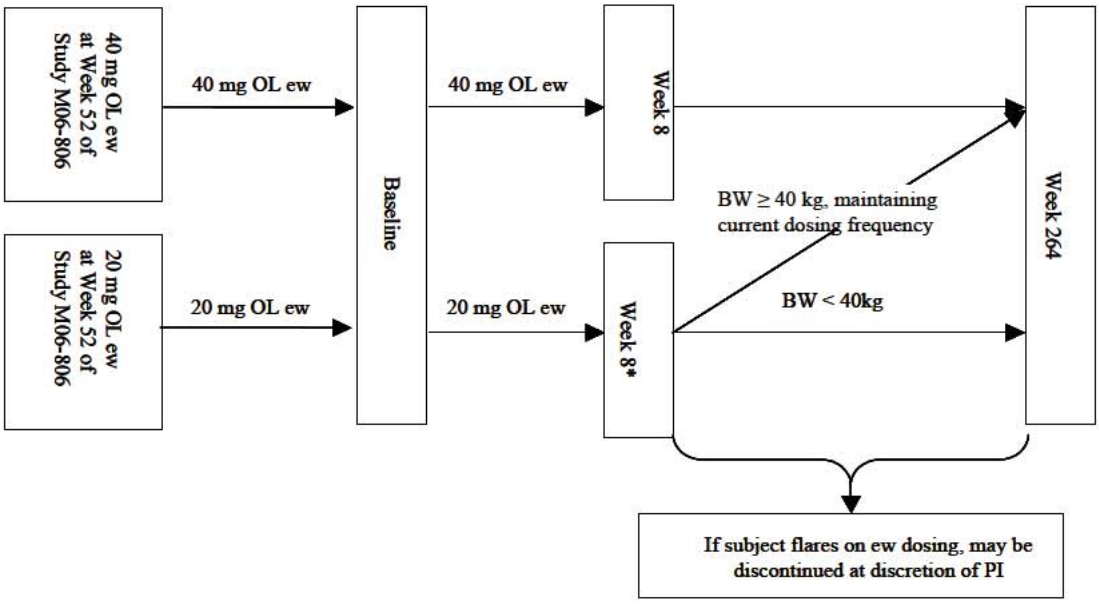
The duration of the study could last up to 264 weeks (approximately 5 years).

Has been changed to read:

The duration of the study could last up to 336 weeks (approximately 6.5 years).

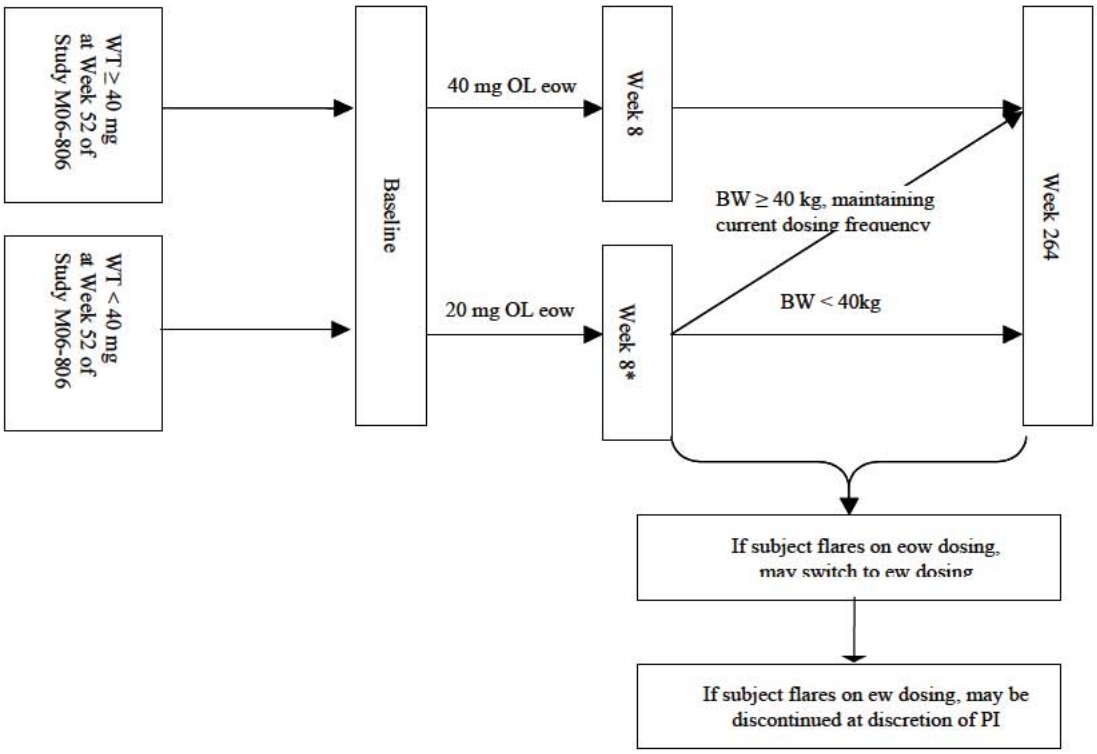
Figure 1. Study Schematic
Previously read:

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator.

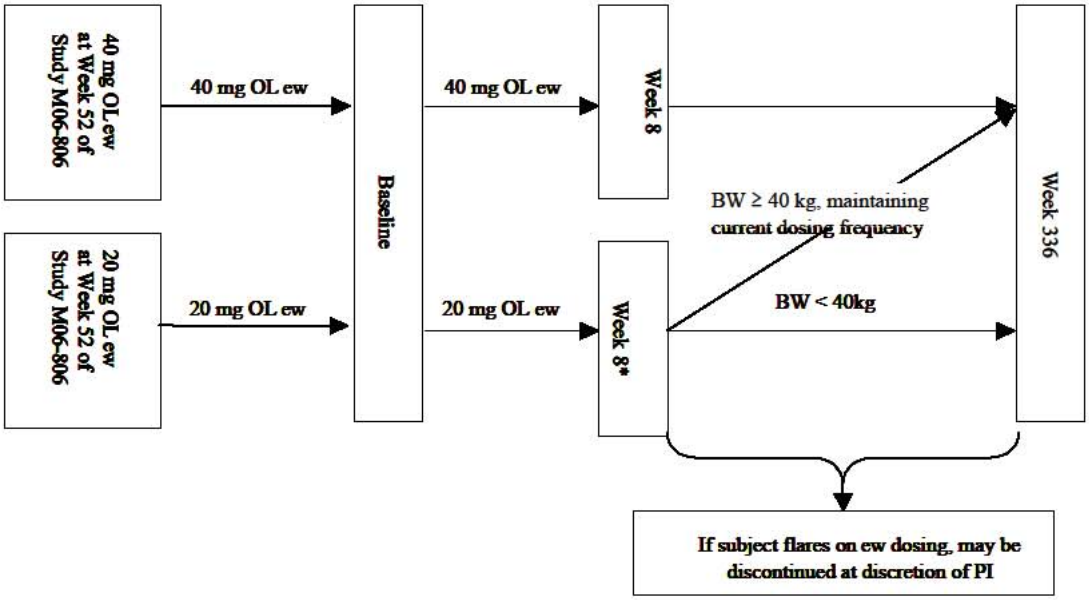
Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



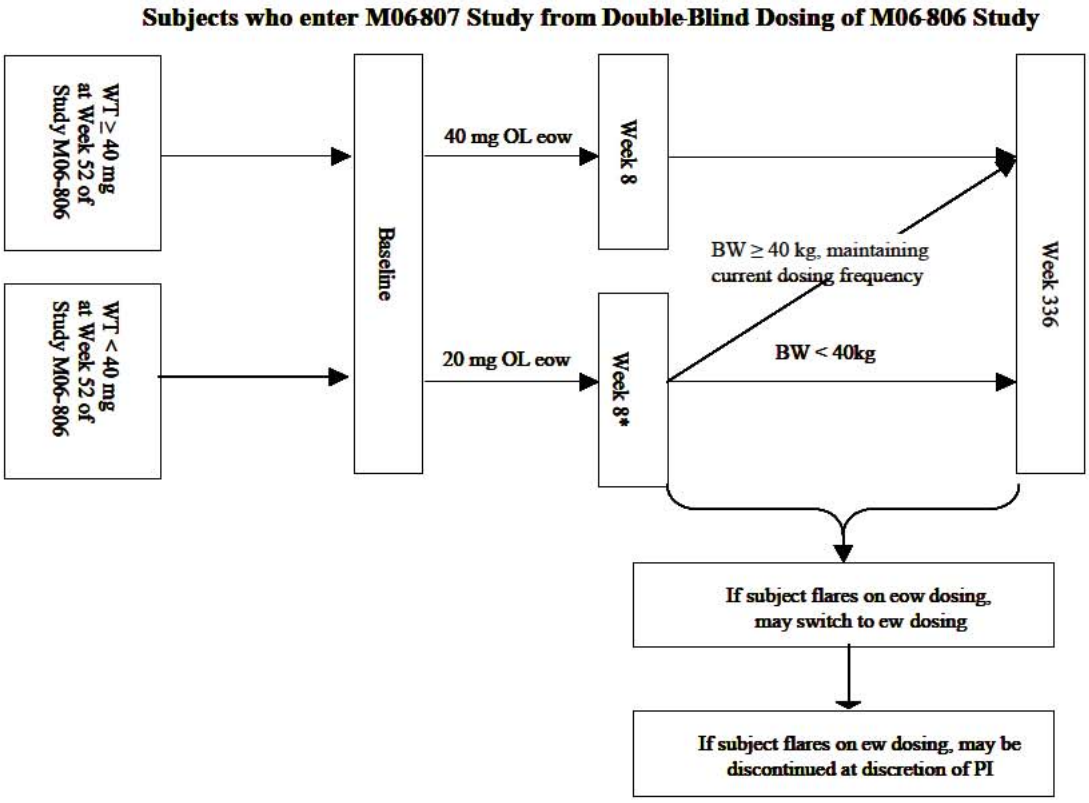
*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Has been changed to read:

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator.



***At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator**

Section 5.2.3.1 Prior Therapy
Add: fifth paragraph

In addition for patients age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate CRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate CRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information

including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate CRF pages.

Section 5.2.3.2 Concomitant Therapy
Second paragraph previously read:

After Week 8, decreases in the dose or discontinuation of Crohns related antibiotics or Crohns related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the AbbVie Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohns related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Has been changed to read:

After Week 8, decreases in the dose or discontinuation of Crohn's related antibiotics or Crohn's related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the AbbVie Medical Monitor. In addition, subjects may be able to initiate or reinitiate Crohn's related treatments, following eight (8) weeks of exposure to open-label adalimumab. Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and total parenteral nutrition (TPN) during the study should be discussed with and approved by the Medical Monitor prior to use.

Section 5.2.3.4 Prohibited Therapy
Third paragraph previously read:

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix L).

Has been changed to read:

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), and any investigational agent are prohibited during the study (see Appendix L).

Table 1. Study Activities
Previously read:

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d,m]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysise	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample[j]					X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d,m]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X		X		X		X		X		X		X	X	
X-ray for bone age[i]			X				X						X		
Serum bone markers[i]	X		X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[l]	

Has been changed to read:

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Inclusion/exclusion criteria	X									
Informed consent	X									
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X
TB testing (PPD or QuantiFERON-TB Gold)[m]							X			
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X	
ANA	X[a]			X						
Anti-dsDNA[f]	X[a]			X						
PCDAI	X[a]	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X	

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X			
Serum bone markers	X[a]				X		X		X	
PK Blood Sample[j]					X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Inclusion/exclusion criteria										
Informed consent										
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X	X	X		X		X		X	
Vital signs[c]	X	X	X		X		X		X	
Physical exam	X	X	X		X		X		X	
General LAB[d]	X	X	X		X		X		X	
TB testing (PPD or QuantiFERON-TB Gold)[m]	X				X				X	
Urinalysis[e]	X	X	X		X		X		X	
Erythrocyte sedimentation rate	X	X	X		X		X		X	
CRP		X			X		X		X	
ANA		X			X				X	
Anti-dsDNA[f]		X			X				X	
PCDAI	X	X	X		X		X		X	
CDAI[g]	X	X	X		X		X		X	
IMPACT III Questionnaire[h]		X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X	X	X		X		X		X	
X-ray for bone age[i]		X			X				X	
Serum bone markers[i]		X	X		X		X		X	
PK Blood Sample[j]	X		X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria													
Informed consent													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X	X	
TB testing (PPD or QuantiFERON-TB Gold)[m]			X				X				X		
Urinalysis[e]	X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X	X	
CRP	X				X		X		X		X		
ANA					X						X		
Anti-dsDNA[f]					X						X		
PCDAI	X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X		X		X		X		X		X	X	
X-ray for bone age[i]					X						X		
Serum bone markers[i]	X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X			X[l]	

Table 1. Study Activities
Footnotes "h." and "m." previously read:

h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264/ET and unscheduled visits.

m. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192 and 240.

Has been changed to read:

h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312 and 336/ET and unscheduled visits.

m. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192, 240, 288 and 336.

Section 5.3.1.1 Study Procedures
First paragraph, last sentence previously read:

The site will call the subjects at Weeks 132, 156, 180, 204, 228 and 252 in order to collect any safety information from the subject as illustrated in Table 1.

Has been changed to read:

The site will call the subjects at Weeks 132, 156, 180, 204, 228, 252, 276, 300 and 324 in order to collect any safety information from the subject as illustrated in Table 1.

Section 5.3.1.1 Study Procedures
Subsection Previous and Concomitant Medications
First paragraph, first sentence previously read:

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 264/ET visit.

Has been changed to read:

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 336/ET visit.

Section 5.3.1.1 Study Procedures
Subsection TB Testing
Second paragraph previously read:

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, and 240.

Has been changed to read:

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, 240, 288 and 336.

Section 5.3.1.1 Study Procedures
Subsection Outcomes
Add: new last paragraph

If a subject is no longer taken care of by their parent or legal guardian, the WPAI-CD should not be completed (neither by the subject's parent or legal guardian nor by the subject himself/herself).

Section 5.3.1.1 Study Procedures
Subsection Adverse Events
First paragraph, first sentence previously read:

Adverse events will be assessed at every study visit from Baseline through the Week 264/ET visit.

Has been changed to read:

Adverse events will be assessed at every study visit from Baseline through the Week 336/ET visit.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Collection of Samples for Adalimumab Analysis
Last paragraph previously read:

A maximum of 13 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Has been changed to read:

A minimum of 14 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

For subjects who have a flare and require switching to higher dose or change dose to ew dosing, up to 2 additional samples are planned to be collected per subject for adalimumab analysis.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Collection of Samples for AAA Analysis
Last paragraph previously read:

A maximum of 13 blood samples are planned to be collected per subject for AAA analysis.

Has been changed to read:

A minimum of 14 blood samples are planned to be collected per subject for AAA analysis.

For subjects who have a flare and require switching to higher dose or change dose to ew dosing, up to 2 additional samples are planned to be collected per subject for AAA analysis.

Section 5.4.1 Discontinuation of Individual Subjects
Second paragraph, first sentence previously read:

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 264/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

Has been changed to read:

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 336/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

Section 5.5.2.1 Packaging and Labeling
Previously read:

The following information will appear on the pre-filled syringe, vial or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of Administration
- Excipients
- Blank spaces to write the subjects identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Has been changed to read:

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4). Each kit will be labeled as required per country requirement. Labels must remain affixed to the kit.

Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Section 6.5 Adverse Event Reporting
First paragraph previously read:

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

Has been changed to read:

In the event of an of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will notify AbbVie within 24 hours of the physician becoming aware of the event by faxing the serious adverse event or non-serious event of malignancy in patients 30 years of age and younger forms to the Immunology Clinical Safety Team.

Section 6.5 Adverse Event Reporting
Last paragraph and in-text table previously read:

For questions regarding SAEs, please contact:

Has been changed to read:

For questions regarding SAEs, please contact:

Section 6.6. Pregnancy
Previously read:

AbbVie must be notified within 1 working day of a sites learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a

study subject will be collected. Upon notification of a pregnancy AbbVie will forward a form to the site, for the Investigator to complete and send back to AbbVie. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to AbbVie.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States, Canada and Puerto Rico. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

Has been changed to read:

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

Section 7.0 Protocol Deviations
In-text table previously read:

[redacted]

Has been changed to read:

[redacted]

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Statistics
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height
Subsection Physical Examination
Third paragraph previously read:

From Baseline to Week 264: use weight from previous visit

Has been changed to read:

From Baseline to Week 336: use weight from previous visit

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height
Subsection Physical Examination
Heading "Item. Height"
Add: new twelfth, thirteenth and last bullets

- From Week 264 to Week 288, use height from Week 240
- From Week 288 to Week 312, use height from Week 264
- From Week 312 to Week 336, use height from Week 288

Appendix P. Subject Dosing Diary
Subsection "Week 264 - Week 288"
Add: new subsection

Week 264 - Week 288

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 264					
	Week 265					
	Week 266					
	Week 267					
	Week 268					
	Week 269					
	Week 270					
	Week 271					
	Week 272					
	Week 273					
	Week 274					
	Week 275					
	Week 276					
	Week 277					
	Week 278					
	Week 279					
	Week 280					
	Week 281					
	Week 282					
	Week 283					
	Week 284					
	Week 285					
	Week 286					
	Week 287					
	Week 288					

Appendix P. Subject Dosing Diary
Subsection "Week 289 - Week 312"
Add: new subsection

Week 289 - Week 312

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 289					
	Week 290					
	Week 291					
	Week 292					
	Week 293					
	Week 294					
	Week 295					
	Week 295					
	Week 296					
	Week 297					
	Week 298					
	Week 299					
	Week 300					
	Week 301					
	Week 302					
	Week 303					
	Week 304					
	Week 305					
	Week 306					
	Week 307					
	Week 308					
	Week 309					
	Week 310					
	Week 311					
	Week 312					

Appendix P. Subject Dosing Diary
Subsection "Week 313 - Week 335"
Add: new subsection

Week 313 - Week 335

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 313					
	Week 314					
	Week 315					
	Week 316					
	Week 317					
	Week 318					
	Week 319					
	Week 320					
	Week 321					
	Week 322					
	Week 323					
	Week 324					
	Week 325					
	Week 326					
	Week 327					
	Week 328					
	Week 329					
	Week 330					
	Week 331					
	Week 332					
	Week 333					
	Week 334					
	Week 335*					

* Week 335 dose will only be taken if on every-week dosing schedule.

Appendix Q Self Injection Instructions
Subsection Study Drug Dosing Schedule
Open-Label (PFS)
Second paragraph previously read:

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

Has been changed to read:

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288 and 312) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

Appendix Q Self Injection Instructions
Subsection Study Drug Dosing Schedule
Vials
Second paragraph previously read:

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

Has been changed to read:

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288 and 312 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

Document Approval

Study M06807 - 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 Crohns Disease Who Have Demonstrated a Clinical Response in the M06-806 Study - Amendment 6 - EudraCT 2007-006494-90 - 12Apr2013

Version: 1.0 **Date:** 15-Apr-2013 12:09:09 PM **Abbott ID:** 04152013-00F9F68032A536-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	12-Apr-2013 04:56:34 PM	Approver
	12-Apr-2013 04:58:52 PM	Approver
	12-Apr-2013 07:29:54 PM	Approver
	12-Apr-2013 07:59:29 PM	Approver
	15-Apr-2013 12:09:07 PM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2, Amendment 1, Administrative Changes 3, 4, 5 and 6, and Amendments 2, 3, 4 and 5

Abbott Number / Investigational Product:	Adalimumab
Date:	03 January 2012
Development Phase:	3
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.
EudraCT Number:	2007-006494-90
Investigator:	Multicenter (Investigator information on file at Abbott Laboratories).
Sponsor:	European Union Countries: Abbott GmbH & Co.KG Knollstrasse 50 67061 Ludwigshafen, Germany Non European Union Countries: Abbott Laboratories, US 100 Abbott Park Road Abbott Park, IL 60064
Emergency Contact:	[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Add in regular TB testing language to protocol.

  Rationale of Change: The FDA required a labeling change ***based on cases of reactivation of TB/occurrence of new TB infections in patients receiving Humira****. The USPI now says retest should be done* ***"periodically"*** *during therapy, without specifying the interval. Based on the actual USPI and on literature search, annual TB rescreening was implemented as a reasonable interval.*

- Correct typo in the vial dosing instructions.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix U.

2.0 Table of Contents

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3.0 Introduction

Crohns Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is

heterogeneous with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohns disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohns disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and

133 subjects continued in a 32-week double blind segment. Clinically significant improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigators Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease. The subject

population will consist of subjects who participated in and successfully completed the M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigators discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigators discretion. For a detailed description of the study please see Section 5.0.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a

responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare is defined as an increase in the Pediatric Crohns Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI score obtained at the subjects previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohns treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohns specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 264 weeks (approximately 5 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohns Disease.
- All applicable local reimbursement procedures are completed.

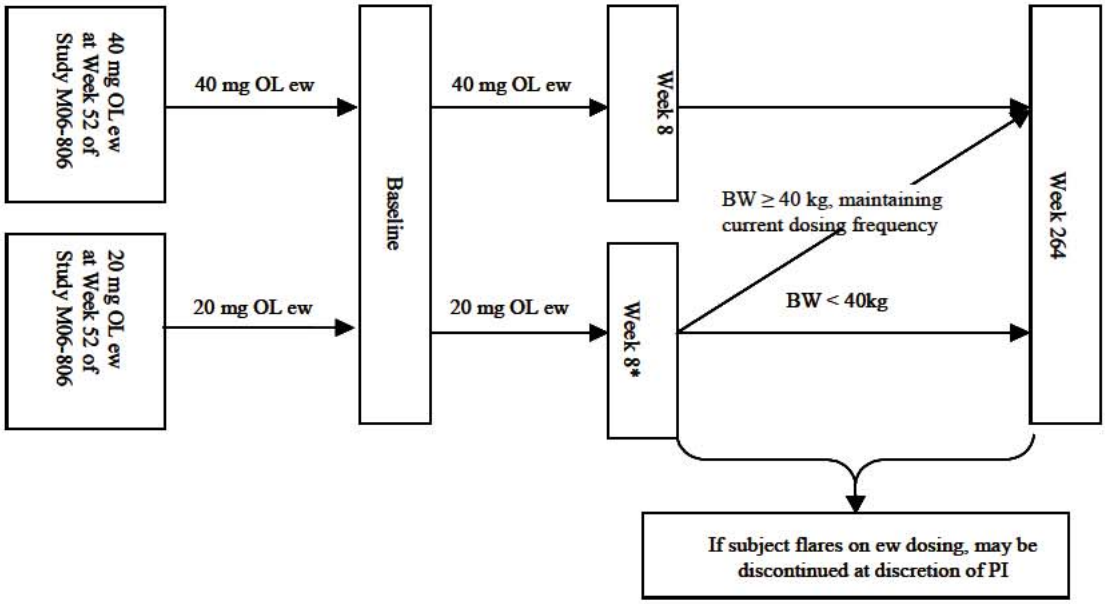
Sites will be notified once these criteria are met.

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

A schematic of the study design is shown in Figure 1 (prior to Amendment 4) and in Figure 2 (after Amendment 4).

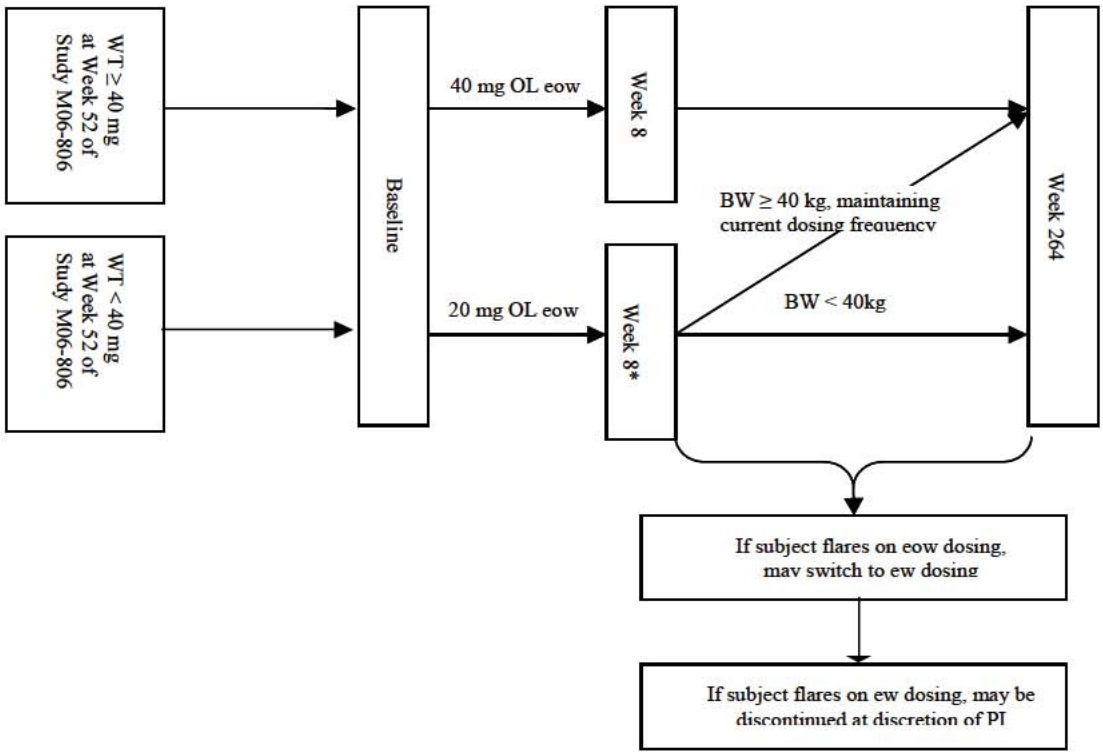
Figure 1. Study Schematic

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



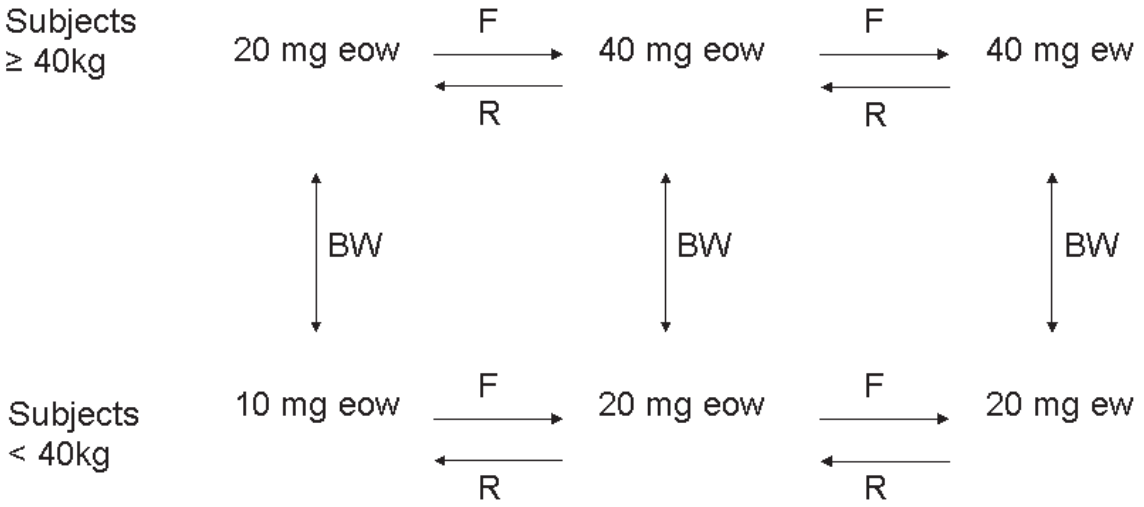
* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Figure 2. Dosing Schematic After Amendment 4



F: Subjects who have a disease flare may be switched to the next higher treatment level.

R: Subjects who responded to their current treatment may be switched to the next lower treatment level at the discretion of the investigator after discussion with the medical monitor. Response is defined as a) a ≥ 15 points decrease in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) a ≥ 15 points decrease in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate.

BW: Subjects with an increase in body weight to ≥ 40 kg may increase their dose to the next higher level at the discretion of the investigator after discussion with the medical monitor. Subjects with a decrease in body weight to < 40 kg may decrease their dose to the next lower level at the discretion of the investigator after discussion with the medical monitor.

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subjects parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subjects diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohns disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma−in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the Abbott Laboratories Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the Abbott Laboratories Medical Monitor identified in Section 7.0

5.2.3.2 Concomitant Therapy

Adjustments of Crohns related concomitant treatments, including Crohns related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohns related antibiotics or Crohns related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the Abbott Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohns related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and Subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg ≤ 10 mg	5 mg/week 2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix L).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d,m]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample[j]					X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d,m]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age[i]			X				X						X		
Serum bone markers[i]	X		X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[l]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264/ET and unscheduled visits.
i. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.
j. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
k. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
l. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.
m. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192 and 240.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228 and 252 in order to collect any safety information from the subject as illustrated in Table 1.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institutions IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of

legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 264/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subjects casebook from the previous study (M06-806). They will not be required to be captured in the subjects casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subjects M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix O) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

TB Testing

For subjects with a negative test at Screening visit from parent study (Study M06-806), an annual PPD or QuantiFERON-TB Gold re-test will be required. If one of the annual

tests has a positive test result, the matter should be discussed with the medical monitor prior to starting any prophylaxis.

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, and 240.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case must be discussed with the Abbott Medical Monitor.

For the PPD test:

- The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The absence of induration should be recorded, as "0 mm," not "negative."
- If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by Abbott prior to use with study subjects.
- If QuantiFERON®-TB Gold (or equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or equivalent) result is indeterminate, this should be considered a positive test result and the case must be discussed with the Abbott Medical Monitor.

In the event both a PPD test and QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test.

Newly initiated prophylactic treatment should be captured in the source documents and on the concomitant medications page in the CRF. Prior therapy should be captured in the appropriate medical history CRF.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of the PPD skin test and the CXR and has to give his/her opinion about the eligibility of each subject to continue in the study. This opinion must be documented in writing in the subject's source documents.

All subjects with a positive PPD need to be approved for continuation in the trial by both the Czech pulmonologist and the Abbott Medical Monitor and all such subjects need to receive prophylaxis for latent TB. Under no circumstances can a subject with a positive PPD result and no prior history of treatment for active or latent TB be allowed to continue in this trial

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be

obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the sites local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured as indicated in Table 1. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohns Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix G. Instructions for completing the PCDAI score is located in Appendix H.

Crohns Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix H.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix I.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1. A copy of the questionnaire is located in Appendix K.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix N, Appendix T).

The subjects parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x−ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by Abbott Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr) / SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Week 264/ET visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s)

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix M for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subjects home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study

drug administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix P.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/- 3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/- 3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06−806).

5.3.2 Drug Concentration Measurements

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collected prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

5.3.2.1 Collection of Samples for Analysis

Collection of Samples for Adalimumab Analysis

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 blood samples are planned to be collected per subject for AAA analysis.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the

assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a −20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

5.3.2.3 Disposition of Samples

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither Abbott nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

5.3.5 Pharmacokinetic Variables

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subjects legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non−melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 264/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subjects condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigators best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

Abbott reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL or in vials containing adalimumab 40 mg/0.8mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

The dose of adalimumab may be decreased to the next lower treatment level as applicable, at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the

previous visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes (used for 40 mg/0.8 mL or 20 mg/0.4 mL doses) and 40 mg/0.8 mL vials (used for 10 mg dose) will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott
Adalimumab	40 mg/0.8 mL (used for 10 mg dose) Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

5.5.2.1 Packaging and Labeling

The following information will appear on the pre-filled syringe, vial or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of Administration
- Excipients
- Blank spaces to write the subjects identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.
Open-label Vials (used for 10 mg dose)	
Open-label kit cartons containing two vials of adalimumab 40 mg/0.8 mL.	

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes and vials are to be stored protected from light at 2° to 8°C/36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until Abbott GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to Abbott Laboratories.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call−in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06−806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The dose of adalimumab may be decreased to the next lower treatment level as applicable at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose

frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix P).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes and vials will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes or vials dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes and vials will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix S. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes and vials will be inventoried by the site and verified by the CRA. The used syringes and vials will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit or vials boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal container to store expelled/used syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes and used vials have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohns disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 before Amendment 4 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD before Amendment 4. A model based on the JRA population was chosen because the body weight range would closely parallel that in a juvenile CD population. Escalation to weekly dosing would provide average

adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provides investigators with the option of dose de-escalation by reducing the dose or switching from ew to eow based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients will have the option to be switched to this dose based on their body weight and clinical status at the discretion of the investigator.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Abbott as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subjects hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subjects usual activities.
Severe	The AE causes considerable interference with the subjects usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

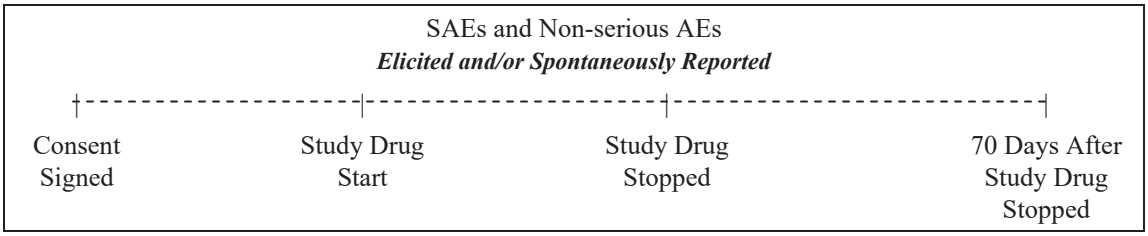
If an Investigators opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

For all sites:

[redacted]

For questions regarding SAEs, please contact:

[redacted]

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohns disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Abbott Laboratories must be notified within 1 working day of a sites learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a study subject will be collected. Upon notification of a pregnancy Abbott will forward a form to the site, for the Investigator to complete and send back to Abbott. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to Abbott.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States, Canada and Puerto Rico. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott representative:

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by Abbott to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind Study M06-806).

8.1.2.2 Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subjects last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

Efficacy will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]
- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be provided to cross-classify and tabulate subjects value from baseline to final value by the presence of clinically significant laboratory results. Each subjects baseline value and final value will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.4.1 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

8.1.5 Interim Analysis

There will be one planned interim analysis. Details of the analysis will be described in the study SAP.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigators Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix C.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to Abbott.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institutions IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subjects parent/legal guardian. The original signed ICF and Assent Form will be placed in the subjects medical record. An entry must also be made in the subjects dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by Abbott. These forms will be used to transmit information collected during the study to Abbott and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by Abbott personnel (or their representatives). Abbott (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by Abbott. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigators meeting will be held with Abbott personnel, the Investigators and their study coordinators, the CROs project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigators meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All data hand entered in the database will be verified by a double-key entry procedure at Abbott. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary

corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

Sites will provide Abbott (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and Abbott Laboratories operations, such as Abbott Laboratories patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of adalimumab. This information may be disclosed as deemed necessary by Abbott Laboratories to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide Abbott Laboratories with complete test results and all

data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by Abbott.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and Abbott. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and Abbott. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to Abbott or their designee.

Abbott may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Abbott terminates the study for safety

reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Abbott will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigators Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subjects last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigators Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title: 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

Protocol Date: 03 January 2012

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

1. Hanauer SB, Sandborn W. Management of Crohns disease in adults. Am J Gastroenterol 2001;96:635-43.

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10. Olafsdottir EJ, Fluge G, Haug K. Chronic inflammatory bowel disease in children in western Norway. J Pediatr Gastroenterol Nutr 1989;8:454-8.

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohns disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form

IRB	Institutional Review Board
ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N−telopeptide
OL	Open-Label
PCDAI	Pediatric Crohns Disease Activity Index
PK	Pharmacokinetics
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohns Disease

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Clinical
		Clinical

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigators agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigators agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigators agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institutions General Assurance Number.

- If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union

Appendix D. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigators qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigators Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix E. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

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Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix F. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Dosing syringes, as applicable

Appendix G. Pediatric Crohns Disease Activity Index (PCDAI)

1.	Abdominal pain rating						**Score**
	- None		= 0 p				
	- Mild - Brief, does not interfere with activities		= 5 p				
	- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p				
2.	Stools (per day)						
	- 0–1 liquid stools, no blood		= 0 p				
	- Up to 2 semi-formed with small blood, or 2–5 liquid		= 5 p				
	- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p				
3.	Patient Functioning, General Well-Being						
	- No limitation of activities, well		= 0 p				
	- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p				
	- Frequent limitation of activity, very poor		= 10 p				
LABORATORY							**Score**
4.	HCT: Male and female ≤ 10 years:			Male 11–14 years:			
		≥ 33	= 0 p		≥35	= 0 p	
		28-32	= 2.5 p		30-34	= 2.5 p	
		< 28	= 5 p		<30	= 5 p	
	Female 11–19 years:	≥ 34	= 0 p	Male 15–19 years:	≥37	= 0 p	
		29-33	= 2.5 p		32-36	= 2.5 p	
		< 29	= 5 p		<32	= 5 p	
5.	ESR (mm/hr)	< 20	= 0 p				
		20-50	= 2.5 p				
		> 50	= 5 p				
6.	Albumin (g/dL)	≥ 3.5	= 0 p				
		3.1-3.4	= 5 p				
		≤ 3.0	= 10 p				

EXAMINATION			**Score**
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥ 10%	= 10 p	
8. Height			
	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations			
(Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)		= 0 p	
- None		= 5 p	
- One		= 10 p	
- ≥ Two			
TOTAL SCORE	**Pediatric Crohns Disease Activity Index (PCDAI)**		

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohns disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohns disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 264: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48
- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216

The intent is to assess the normalcy vs. impairment of the subjects recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

$$\frac{\text{Present height} - \text{Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

    a. Velocity less than "Minus 2 SD" scores 10 points.

    b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

    c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	Minus 2SD	Minus 1SD	Mean
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix I. Crohns Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0=none, 1=mild, 2=moderate, 3=severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0=generally well, 1=slightly underpar, 2=poor, 3=very poor, 4=terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil / Imodium / Loperamide /opiates for diarrhea 0=no, 1=yes	_____	X	30	
6. Abdominal mass 0=none, 2=questionable, 5=defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix J. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. Add item requested for each day.	Crohns Disease Activity Index Subject Diary Card						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0=none, 1=mild, 2=moderate, 3=severe)							
Daily rating of general well being. (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)							

Subject Initials:_____ Subjects Signature:_____

Investigator or Designees Signature:_____

Appendix K. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohns disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I dont feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I dont think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I dont try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I dont feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix L. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix M. Day 70 Phone Call

Site Name / Number: _____

Subject Number:_____

Subject Initials:_____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to Abbott within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted]

Appendix N. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohns disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix O. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctors office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix P. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctors office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctors office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13- Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263*					

* Week 263 dose will only be taken if on every-week dosing schedule.

Appendix Q. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

For 40 mg dose, one pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 20 mg dose, one pre-filled syringe will contain 0.4 mL of liquid. The total available dose is 0.4 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

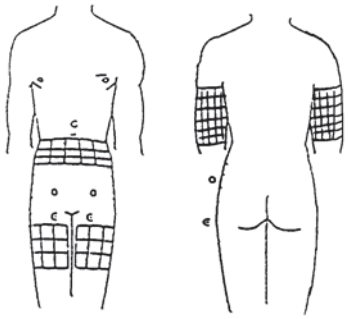
Remember to complete your dosing diary after each injection and to call the doctors office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

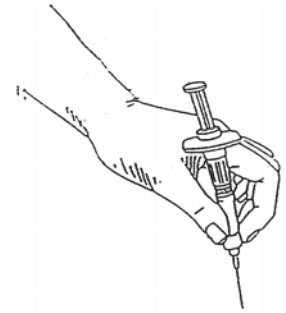
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



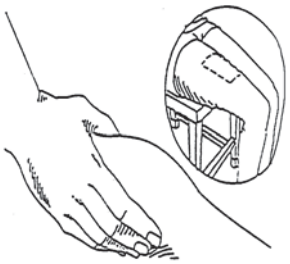
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

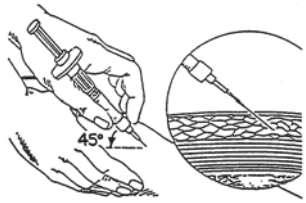


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

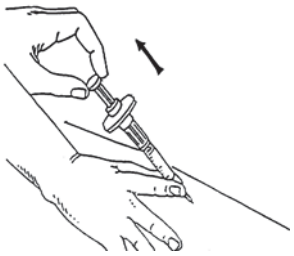
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

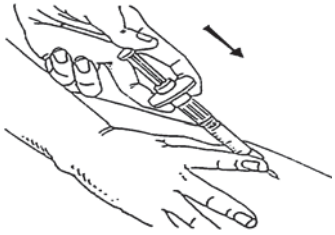


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



11. Remove needle while maintaining a 45-degree angle.

12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Self Injection Instructions

Subject Instructions

0.2 mL dose

Vials

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Vials**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

The total dose is 0.2 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 10 mg dose, 0.2 mL of the solution is drawn from a vial containing adalimumab 40 mg/0.8 mL solution. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused vials to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused vials should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information **Vials**

- Vials will be labeled "adalimumab."
- Store all adalimumab vials in your refrigerator NOT in the freezer. Should the vials accidentally become frozen, call your study coordinator.
- 0.2 mL = 0.2 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW VIAL EVERY INJECTION DAY.** There will be medication left in the vial. **DO NOT RE-USE.**
- Save all study drugs. ***Vials (used and unused) must be returned to the study center at each visit.*** Used vials and syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

Injection Instructions **Vials**

Select a clean, well-lit, flat surface.

1. Wash your hands thoroughly with soap and warm water. It is important to keep your work surface as clean as possible.

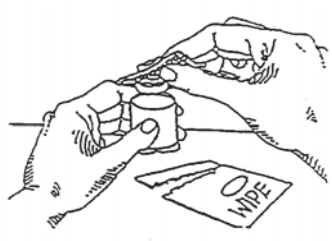
2. Open carton.

3. Examine the carton and components in it to make sure they are complete.

   - One or two vials containing adalimumab

4. Remove the plastic cap from the vial.

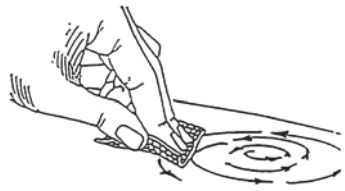
5. Wipe the gray stopper with an alcohol swab and discard alcohol swab.



6. Place the vial upright on a hard, flat surface.

7. Choose an injection site on the upper thigh or abdomen.

8. Prepare the injection site by wiping it thoroughly with a second alcohol swab. Use a circular motion.



9. Remove the needle cover from the syringe. *(The needle is sterile, so be very careful not to touch the needle or allow it to touch any surface.)*

10. Draw the plunger on the syringe back.

11. With the vial sitting on a hard, flat surface, insert needle straight down through the center of the gray stopper. If the needle is correctly lined up, you should feel slight resistance and then a "pop" as the needle penetrates the center of the stopper. (*Be careful not to insert the needle at an angle as this may cause the needle to bend. If the needle is not correctly aligned, you will feel constant resistance as it penetrates the stopper and will not feel a "pop.")*

12. Push the plunger in forcing air into the vial.

13. With the needle still in place, turn the vial upside down. Keeping the vial at eye level, slowly pull the plunger back to draw the liquid into the syringe. This will cause the bubbles to rise to the top of the syringe. *(As the liquid level in the vial drops, you may have to withdraw the needle partially to keep the tip of the needle in the liquid.)* Only 0.2 mL of the vial will be drawn into the syringe.

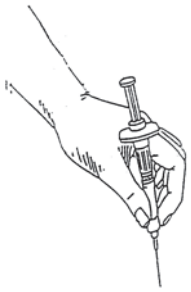
14. With the needle still in the vial, check the syringe for air bubbles. To remove any air bubbles, start by gently tapping the syringe.

15. Slowly press the plunger to push any bubbles out of the syringe and into the vial. *(If you accidentally push any liquid back into the vial, draw the liquid back into the syringe and check again for air bubbles. It's okay for a small amount of liquid to remain in the vial.)*

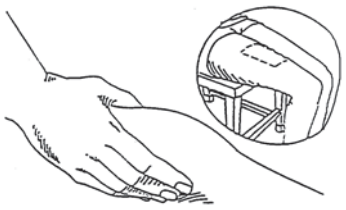
16. Withdraw the needle from the vial, being careful not to touch it to any surface.

Vials

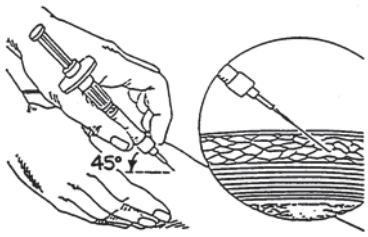
17. Take the syringe in one hand.



18. With your other hand, firmly pinch the skin around the cleaned injection site. *(Be careful not to touch the cleaned area.)*



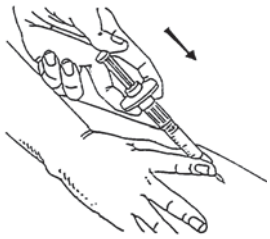
19. Hold the syringe at about a 45-degree angle to the skin and use a quick, short motion to push the needle into the skin.



20. Once the needle is in, release the skin.

Vials

21. While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. Only 0.2 mL of the vial will be injected.



22. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same 45-degree angle.

23. Dispose of both the needle and syringe in a puncture-resistant container, or sharps container, which will be provided.

24. You may want to press a cotton ball on the injection site for 10 seconds. If there is some slight bleeding, you may choose to apply a small bandage.

25. Return the vial into the original packaging.

26. Place the medication kit back into the refrigerator.

Vials

EACH TIME YOU RECEIVE AN INJECTION OF STUDY MEDICATION, REMEMBER TO RECORD THE INFORMATION ON YOUR DOSING SHEET.

GENERAL INFORMATION:

27. ROTATING INJECTION SITES IS RECOMMENDED. PLEASE DO NOT INJECT THE STUDY MEDICATION INTO A PRIOR SITE OF INJECTION.

28. Store all of your drug in the refrigerator. Should the vials become accidentally frozen or left out, call your study coordinator. DO NOT USE THESE VIALS.

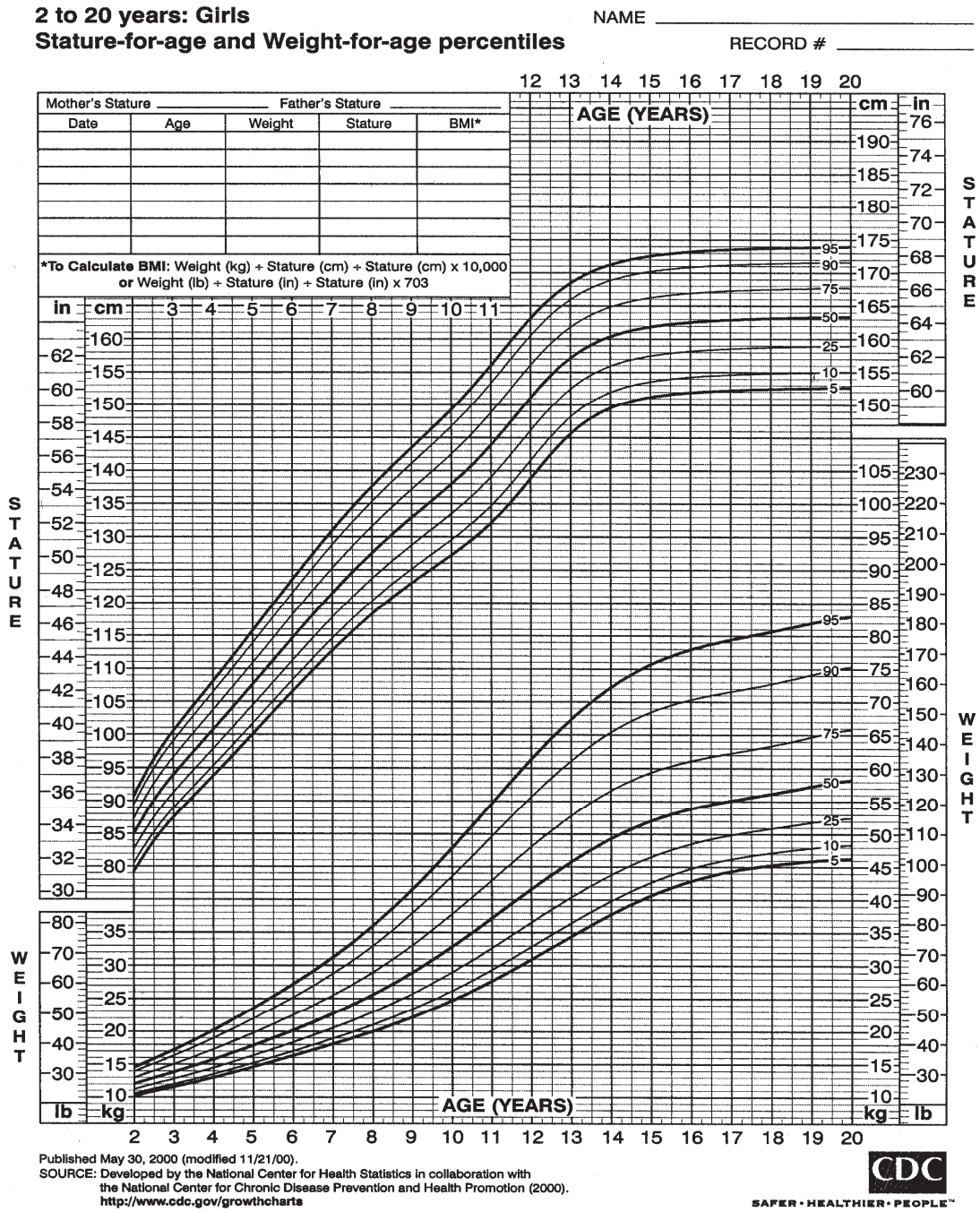
29. If you forget to take the drug or make a mistake with an injection, please call your study coordinator.

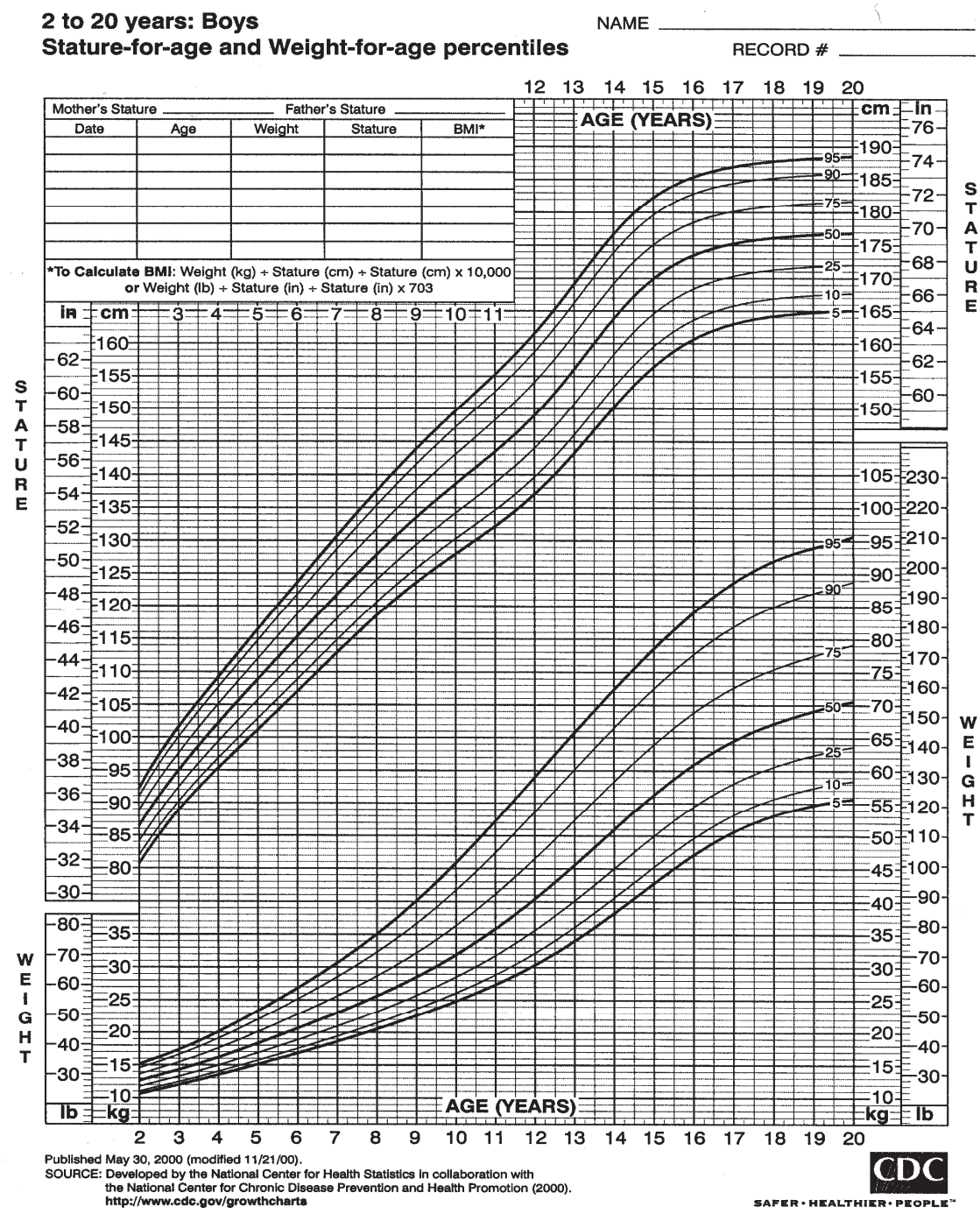
30. Please save all of your study medication, even if you skip a dose. Please bring all used and unused vials back to the physician at your next study visit.

31. There will be study medication remaining in the vials. DO NOT USE THE MEDICATION LEFT IN THE VIAL. Please return the vial along with the remaining study medication back to the physician at your next study visit.

32. Specific side effects to watch for: redness and swelling at the injection site. Please tell the study coordinator if you have any side effects from injecting the drug.

Appendix R. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER · HEALTHIER · PEOPLE™

Appendix S. Subject Abbott Laboratories Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix T. Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) - Caregiver

The following questions ask about the effect of your childs Crohns disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

---

2. During the past seven days, how many hours did you miss from work because of problems associated with your childs Crohns disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your childs Crohns disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your childs Crohns disease affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your childs Crohns disease *affected your work only a little, choose a low number. Choose a high number if your childs* Crohns disease *affected your work a great deal.*

Consider only how much your childs Crohns disease affected your productivity while you were working.

My childs Crohns disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your childs Crohns Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your childs Crohns Disease affected your activities only a little, choose a low number. Choose a high number if your childs Crohns Disease affected your activities a great deal.

Consider only how much your childs Crohns disease affected your ability to do your regular daily activities, other than work at a job.

My childs Crohns disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:CD-Caregiver (US English)

Appendix U. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Table 1. Study Activities
Add: Footnote "m."

m. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192 and 240.

Section 5.3.1.1 Study Procedures
Add: Subsection TB Testing

TB Testing

For subjects with a negative test at Screening visit from parent study (Study M06-806), an annual PPD or QuantiFERON-TB Gold re-test will be required. If one of the annual tests has a positive test result, the matter should be discussed with the medical monitor prior to starting any prophylaxis.

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit after the amended protocol is approved by IRB/IEC including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches one of the scheduled visits: Weeks 48, 96, 144, 192, and 240.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case must be discussed with the Abbott Medical Monitor.

For the PPD test:

- The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The absence of induration should be recorded, as "0 mm," not "negative."
- If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by Abbott prior to use with study subjects.
- If QuantiFERON®-TB Gold (or equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or equivalent) result is indeterminate, this should be considered a positive test result and the case must be discussed with the Abbott Medical Monitor.

In the event both a PPD test and QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test.

Newly initiated prophylactic treatment should be captured in the source documents and on the concomitant medications page in the CRF. Prior therapy should be captured in the appropriate medical history CRF.

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.

- A pulmonologist must review the results of the PPD skin test and the CXR and has to give his/her opinion about the eligibility of each subject to continue in the study. This opinion must be documented in writing in the subject's source documents.

All subjects with a positive PPD need to be approved for continuation in the trial by both the Czech pulmonologist and the Abbott Medical Monitor and all such subjects need to receive prophylaxis for latent TB. Under no circumstances can a subject with a positive PPD result and no prior history of treatment for active or latent TB be allowed to continue in this trial

Appendix Q. Self Injection Instructions
Subsection "Injection Instructions"
Item 21 previously read:

While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. For subjects that weigh ≥ 40 kg, all 0.8 mL will be injected. For subjects that weigh < 40 kg, only 0.4 mL of the vial will be injected.

Has been changed to read:

While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. Only 0.2 mL of the vial will be injected.

Document Approval

Study M06807 - 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 Crohns Disease Who Have Demonstrated a Clinical Response in the M06-806 Study - Amendment 5 - EudraCT 2007-006494-90 - 03Jan2012

Version: 1.0 **Date:** 04-Jan-2012 10:48:50 AM **Abbott ID:** 01042012-00AB61A00D5DD4-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	03-Jan-2012 10:33:48 PM	Author
	03-Jan-2012 10:50:18 PM	Approver
	03-Jan-2012 11:08:34 PM	Approver
	04-Jan-2012 10:48:50 AM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2, Amendment 1, Administrative Changes 3, 4, 5 and 6, and Amendments 2, 3 and 4

Abbott Number / Investigational Product:	Adalimumab
Date:	29 June 2011
Development Phase:	3
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.
EudraCT Number:	2007-006494-90
Investigator:	Multicenter (Investigator information on file at Abbott Laboratories).
Sponsor:	European Union Countries: Abbott GmbH & Co.KG Knollstrasse 50 67061 Ludwigshafen, Germany Non European Union Countries: Abbott Laboratories, US 100 Abbott Park Road Abbott Park, IL 60064
Emergency Contact:	[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Allow dose and frequency decrease in subjects who have responded well to treatment, allow dose adjustment due to weight loss and add 10 mg eow dosage.
    - After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provides investigators with the option of dose de-escalation by reducing the dose or dose frequency (i.e., switching from ew to eow) based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients will have the option to be switched to this dose based on their body weight and clinical status at the discretion of the investigator.
    - If subjects experience a flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to the next higher treatment level.
- Correct typographical errors.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix U.

2.0 Table of Contents

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3.0 Introduction

Crohns Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is

heterogeneous with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohns disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohns disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and

133 subjects continued in a 32-week double blind segment. Clinically significant improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigators Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease. The subject

population will consist of subjects who participated in and successfully completed the M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigators discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigators discretion. For a detailed description of the study please see Section 5.0.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a

responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare is defined as an increase in the Pediatric Crohns Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI score obtained at the subjects previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohns treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohns specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 264 weeks (approximately 5 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohns Disease.
- All applicable local reimbursement procedures are completed.

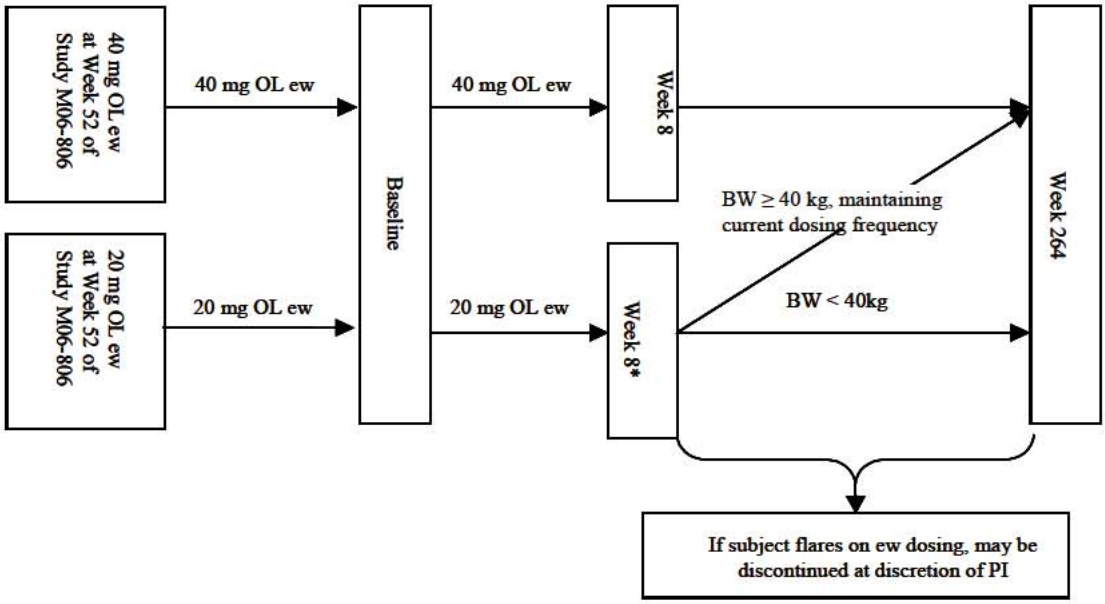
Sites will be notified once these criteria are met.

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

A schematic of the study design is shown in Figure 1 (prior to Amendment 4) and in Figure 2 (after Amendment 4).

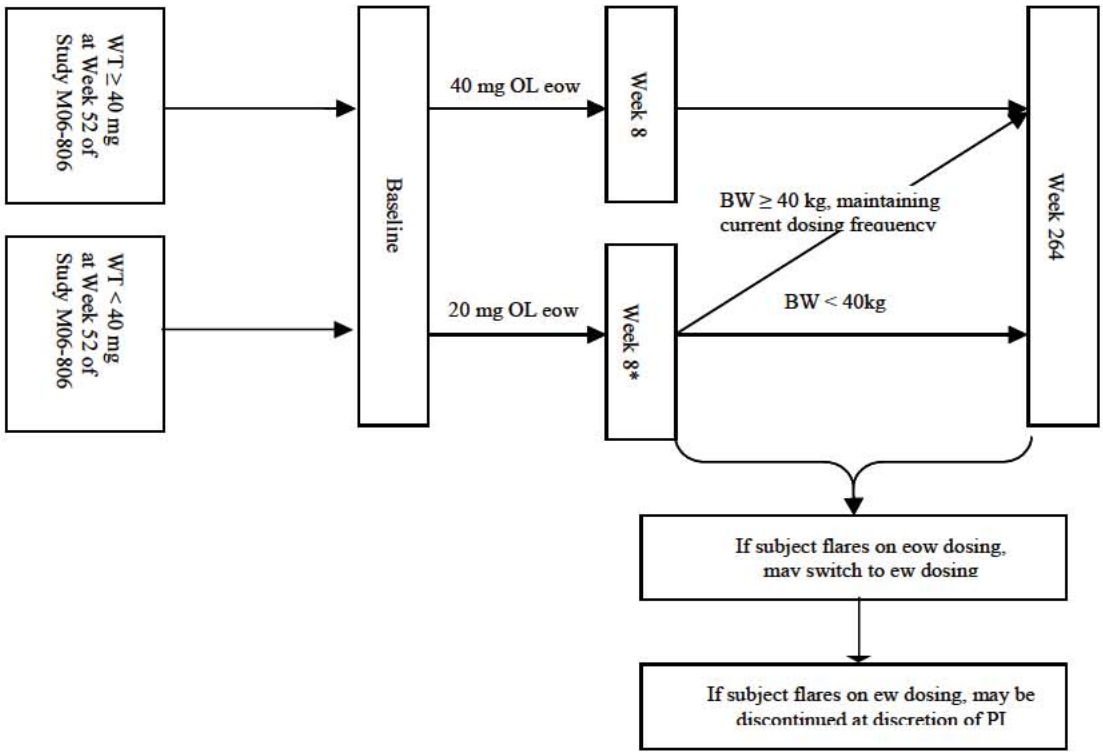
Figure 1. Study Schematic

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



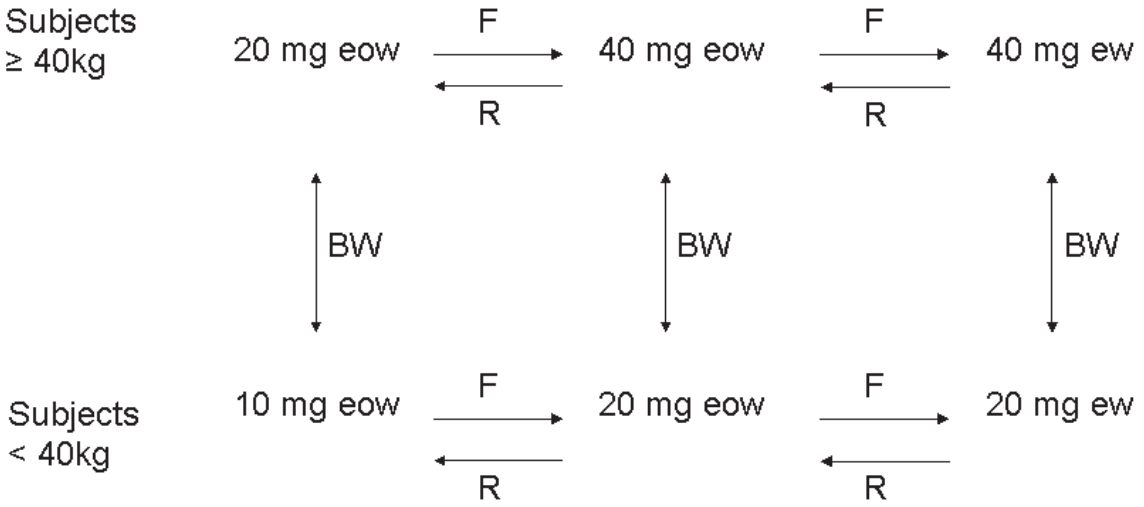
* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Figure 2. Dosing Schematic After Amendment 4



F: Subjects who have a disease flare may be switched to the next higher treatment level.

R: Subjects who responded to their current treatment may be switched to the next lower treatment level at the discretion of the investigator after discussion with the medical monitor. Response is defined as a) a ≥ 15 points decrease in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) a ≥ 15 points decrease in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate.

BW: Subjects with an increase in body weight to ≥ 40 kg may increase their dose to the next higher level at the discretion of the investigator after discussion with the medical monitor. Subjects with a decrease in body weight to < 40 kg may decrease their dose to the next lower level at the discretion of the investigator after discussion with the medical monitor.

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subjects parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subjects diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohns disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma−in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the

opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the Abbott Laboratories Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the Abbott Laboratories Medical Monitor identified in Section 7.0

5.2.3.2 Concomitant Therapy

Adjustments of Crohns related concomitant treatments, including Crohns related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohns related antibiotics or Crohns related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the Abbott Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohns related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and Subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg ≤ 10 mg	5 mg/week 2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix L).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample[j]					X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age[i]			X				X						X		
Serum bone markers[i]	X		X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[l]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264/ET and unscheduled visits.
i. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.
j. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
k. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
l. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228 and 252 in order to collect any safety information from the subject as illustrated in Table 1.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institutions IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of

legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 264/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subjects casebook from the previous study (M06-806). They will not be required to be captured in the subjects casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subjects M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix O) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the sites local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured as indicated in Table 1. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohns Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix G. Instructions for completing the PCDAI score is located in Appendix H.

Crohns Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix H.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix I.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1. A copy of the questionnaire is located in Appendix K.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix N, Appendix T).

The subjects parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x−ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by Abbott Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr) / SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Week 264/ET visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s)

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix M for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subjects home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study

drug administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix P.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/- 3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/- 3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06−806).

5.3.2 Drug Concentration Measurements

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collected prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

5.3.2.1 Collection of Samples for Analysis

Collection of Samples for Adalimumab Analysis

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 blood samples are planned to be collected per subject for AAA analysis.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the

assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a −20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

5.3.2.3 Disposition of Samples

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither Abbott nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

5.3.5 Pharmacokinetic Variables

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subjects legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non−melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 264/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subjects condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigators best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

Abbott reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL or in vials containing adalimumab 40 mg/0.8mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

The dose of adalimumab may be decreased to the next lower treatment level as applicable, at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the

previous visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes (used for 40 mg/0.8 mL or 20 mg/0.4 mL doses) and 40 mg/0.8 mL vials (used for 10 mg dose) will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott
Adalimumab	40 mg/0.8 mL (used for 10 mg dose) Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

5.5.2.1 Packaging and Labeling

The following information will appear on the pre-filled syringe, vial or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of Administration
- Excipients
- Blank spaces to write the subjects identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.
Open-label Vials (used for 10 mg dose)	
Open-label kit cartons containing two vials of adalimumab 40 mg/0.8 mL.	

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes and vials are to be stored protected from light at 2° to 8°C/36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until Abbott GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to Abbott Laboratories.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call−in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06−806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The dose of adalimumab may be decreased to the next lower treatment level as applicable at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose

frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix P).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes and vials will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes or vials dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes and vials will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix S. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes and vials will be inventoried by the site and verified by the CRA. The used syringes and vials will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit or vials boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal container to store expelled/used syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes and used vials have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohns disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 before Amendment 4 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD before Amendment 4. A model based on the JRA population was chosen because the body weight range would closely parallel that in a juvenile CD population. Escalation to weekly dosing would provide average

adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provides investigators with the option of dose de-escalation by reducing the dose or switching from ew to eow based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients will have the option to be switched to this dose based on their body weight and clinical status at the discretion of the investigator.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Abbott as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subjects hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subjects usual activities.
Severe	The AE causes considerable interference with the subjects usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

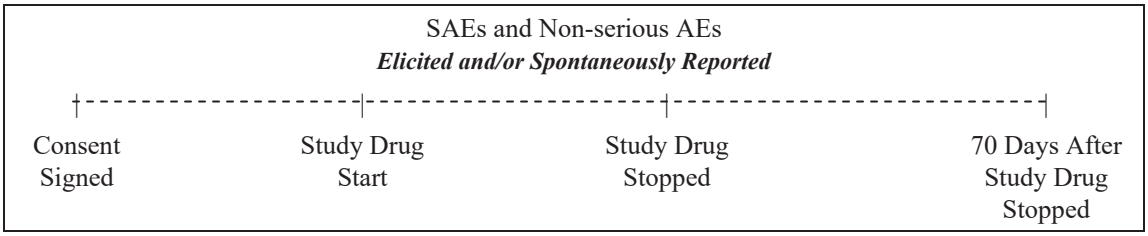
If an Investigators opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

For all sites:

[redacted]

For questions regarding SAEs, please contact:

[redacted]

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohns disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Abbott Laboratories must be notified within 1 working day of a sites learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a study subject will be collected. Upon notification of a pregnancy Abbott will forward a form to the site, for the Investigator to complete and send back to Abbott. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to Abbott.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States, Canada and Puerto Rico. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott representative:

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by Abbott to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind Study M06-806).

8.1.2.2 Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subjects last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

Efficacy will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]
- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be provided to cross-classify and tabulate subjects value from baseline to final value by the presence of clinically significant laboratory results. Each subjects baseline value and final value will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.4.1 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

8.1.5 Interim Analysis

There will be one planned interim analysis. Details of the analysis will be described in the study SAP.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigators Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix C.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to Abbott.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institutions IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subjects parent/legal guardian. The original signed ICF and Assent Form will be placed in the subjects medical record. An entry must also be made in the subjects dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by Abbott. These forms will be used to transmit information collected during the study to Abbott and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by Abbott personnel (or their representatives). Abbott (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by Abbott. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigators meeting will be held with Abbott personnel, the Investigators and their study coordinators, the CROs project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigators meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All data hand entered in the database will be verified by a double-key entry procedure at Abbott. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary

corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

Sites will provide Abbott (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and Abbott Laboratories operations, such as Abbott Laboratories patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of adalimumab. This information may be disclosed as deemed necessary by Abbott Laboratories to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide Abbott Laboratories with complete test results and all

data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by Abbott.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and Abbott. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and Abbott. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to Abbott or their designee.

Abbott may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Abbott terminates the study for safety

reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Abbott will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigators Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subjects last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigators Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title: 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

Protocol Date: 29 June 2011

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohns disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form

IRB	Institutional Review Board
ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N−telopeptide
OL	Open-Label
PCDAI	Pediatric Crohns Disease Activity Index
PK	Pharmacokinetics
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohns Disease

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Clinical
		Clinical

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigators agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigators agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigators agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institutions General Assurance Number.

- If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union

Appendix D. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigators qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigators Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix E. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB *Elimination*

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

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Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix F. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Dosing syringes, as applicable

Appendix G. Pediatric Crohns Disease Activity Index (PCDAI)

1.	Abdominal pain rating						**Score**
	- None		= 0 p				
	- Mild - Brief, does not interfere with activities		= 5 p				
	- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p				
2.	Stools (per day)						
	- 0–1 liquid stools, no blood		= 0 p				
	- Up to 2 semi-formed with small blood, or 2–5 liquid		= 5 p				
	- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p				
3.	Patient Functioning, General Well-Being						
	- No limitation of activities, well		= 0 p				
	- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p				
	- Frequent limitation of activity, very poor		= 10 p				
LABORATORY							**Score**
4.	HCT: Male and female ≤ 10 years:			Male 11–14 years:			
		≥ 33	= 0 p		≥35	= 0 p	
		28-32	= 2.5 p		30-34	= 2.5 p	
		< 28	= 5 p		<30	= 5 p	
	Female 11–19 years:	≥ 34	= 0 p	Male 15–19 years:	≥37	= 0 p	
		29-33	= 2.5 p		32-36	= 2.5 p	
		< 29	= 5 p		<32	= 5 p	
5.	ESR (mm/hr)	< 20	= 0 p				
		20-50	= 2.5 p				
		> 50	= 5 p				
6.	Albumin (g/dL)	≥ 3.5	= 0 p				
		3.1-3.4	= 5 p				
		≤ 3.0	= 10 p				

EXAMINATION			**Score**
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥ 10%	= 10 p	
8. Height			
	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations			
(Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)		= 0 p	
- None		= 5 p	
- One		= 10 p	
- ≥ Two			
TOTAL SCORE	**Pediatric Crohns Disease Activity Index (PCDAI)**		

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohns disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohns disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 264: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48
- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216

The intent is to assess the normalcy vs. impairment of the subjects recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

$$\frac{\text{Present height} - \text{Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

    a. Velocity less than "Minus 2 SD" scores 10 points.

    b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

    c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	Minus 2SD	Minus 1SD	Mean
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix I. Crohns Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0=none, 1=mild, 2=moderate, 3=severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0=generally well, 1=slightly underpar, 2=poor, 3=very poor, 4=terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil / Imodium / Loperamide /opiates for diarrhea 0=no, 1=yes	_____	X	30	
6. Abdominal mass 0=none, 2=questionable, 5=defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix J. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. **Add item requested for each day.**	**Crohns Disease Activity Index Subject Diary Card**						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0=none, 1=mild, 2=moderate, 3=severe)							
Daily rating of general well being. (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)							

Subject Initials:_____ Subjects Signature:_____

Investigator or Designees Signature:_____

Appendix K. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohns disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I dont feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I dont think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I dont try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I dont feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix L. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix M. Day 70 Phone Call

Site Name / Number: _____

Subject Number:_____

Subject Initials:_____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to Abbott within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted]

Appendix N. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohns disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix O. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctors office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix P. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctors office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctors office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13- Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263*					

* Week 263 dose will only be taken if on every-week dosing schedule.

Appendix Q. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

For 40 mg dose, one pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 20 mg dose, one pre-filled syringe will contain 0.4 mL of liquid. The total available dose is 0.4 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

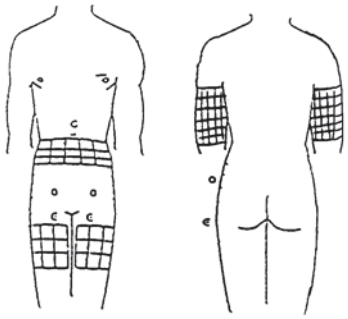
Remember to complete your dosing diary after each injection and to call the doctors office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

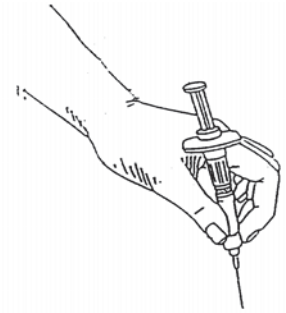
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



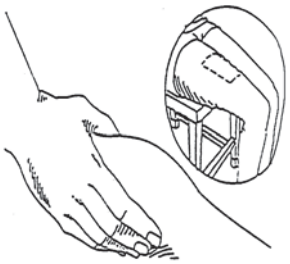
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

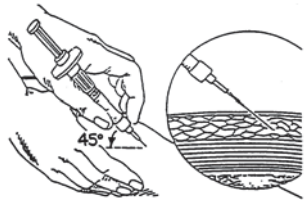


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

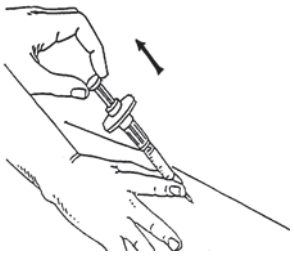
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

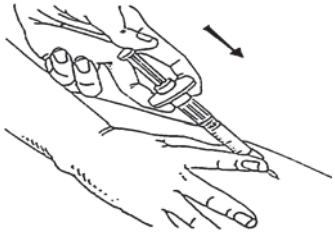


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



11. Remove needle while maintaining a 45-degree angle.

12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Self Injection Instructions

Subject Instructions

0.2 mL dose

Vials

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Vials**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

The total dose is 0.2 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 10 mg dose, 0.2 mL of the solution is drawn from a vial containing adalimumab 40 mg/0.8 mL solution. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused vials to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused vials should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information **Vials**

- Vials will be labeled "adalimumab."
- Store all adalimumab vials in your refrigerator NOT in the freezer. Should the vials accidentally become frozen, call your study coordinator.
- 0.2 mL = 0.2 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW VIAL EVERY INJECTION DAY.** There will be medication left in the vial. **DO NOT RE-USE.**
- Save all study drugs. ***Vials (used and unused) must be returned to the study center at each visit.*** Used vials and syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

Injection Instructions **Vials**

Select a clean, well-lit, flat surface.

1. Wash your hands thoroughly with soap and warm water. It is important to keep your work surface as clean as possible.

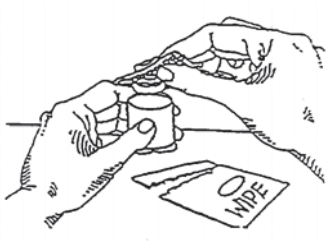
2. Open carton.

3. Examine the carton and components in it to make sure they are complete.

   - One or two vials containing adalimumab

4. Remove the plastic cap from the vial.

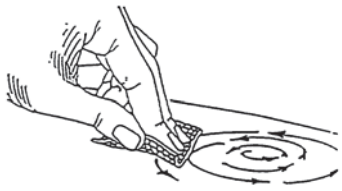
5. Wipe the gray stopper with an alcohol swab and discard alcohol swab.



6. Place the vial upright on a hard, flat surface.

7. Choose an injection site on the upper thigh or abdomen.

8. Prepare the injection site by wiping it thoroughly with a second alcohol swab. Use a circular motion.



9. Remove the needle cover from the syringe. *(The needle is sterile, so be very careful not to touch the needle or allow it to touch any surface.)*

10. Draw the plunger on the syringe back.

11. With the vial sitting on a hard, flat surface, insert needle straight down through the center of the gray stopper. If the needle is correctly lined up, you should feel slight resistance and then a "pop" as the needle penetrates the center of the stopper. (*Be careful not to insert the needle at an angle as this may cause the needle to bend. If the needle is not correctly aligned, you will feel constant resistance as it penetrates the stopper and will not feel a "pop.")*

12. Push the plunger in forcing air into the vial.

13. With the needle still in place, turn the vial upside down. Keeping the vial at eye level, slowly pull the plunger back to draw the liquid into the syringe. This will cause the bubbles to rise to the top of the syringe. *(As the liquid level in the vial drops, you may have to withdraw the needle partially to keep the tip of the needle in the liquid.)* Only 0.2 mL of the vial will be drawn into the syringe.

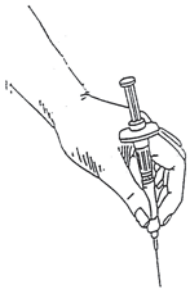
14. With the needle still in the vial, check the syringe for air bubbles. To remove any air bubbles, start by gently tapping the syringe.

15. Slowly press the plunger to push any bubbles out of the syringe and into the vial. *(If you accidentally push any liquid back into the vial, draw the liquid back into the syringe and check again for air bubbles. It's okay for a small amount of liquid to remain in the vial.)*

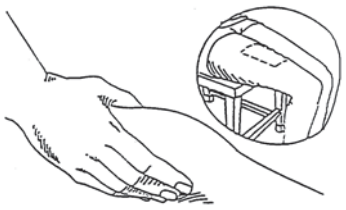
16. Withdraw the needle from the vial, being careful not to touch it to any surface.

Vials

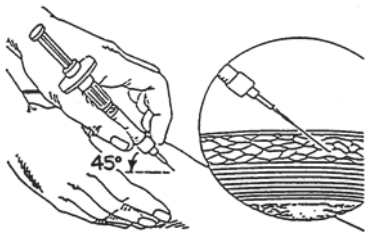
17. Take the syringe in one hand.



18. With your other hand, firmly pinch the skin around the cleaned injection site. *(Be careful not to touch the cleaned area.)*



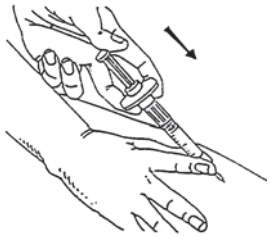
19. Hold the syringe at about a 45-degree angle to the skin and use a quick, short motion to push the needle into the skin.



20. Once the needle is in, release the skin.

Vials

21. While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. For subjects that weigh ≥ 40 kg, all 0.8 mL will be injected. For subjects that weigh < 40 kg, only 0.4 mL of the vial will be injected.



22. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same 45-degree angle.

23. Dispose of both the needle and syringe in a puncture-resistant container, or sharps container, which will be provided.

24. You may want to press a cotton ball on the injection site for 10 seconds. If there is some slight bleeding, you may choose to apply a small bandage.

25. Return the vial into the original packaging.

26. Place the medication kit back into the refrigerator.

Vials

EACH TIME YOU RECEIVE AN INJECTION OF STUDY MEDICATION, REMEMBER TO RECORD THE INFORMATION ON YOUR DOSING SHEET.

GENERAL INFORMATION:

27. ROTATING INJECTION SITES IS RECOMMENDED. PLEASE DO NOT INJECT THE STUDY MEDICATION INTO A PRIOR SITE OF INJECTION.

28. Store all of your drug in the refrigerator. Should the vials become accidentally frozen or left out, call your study coordinator. DO NOT USE THESE VIALS.

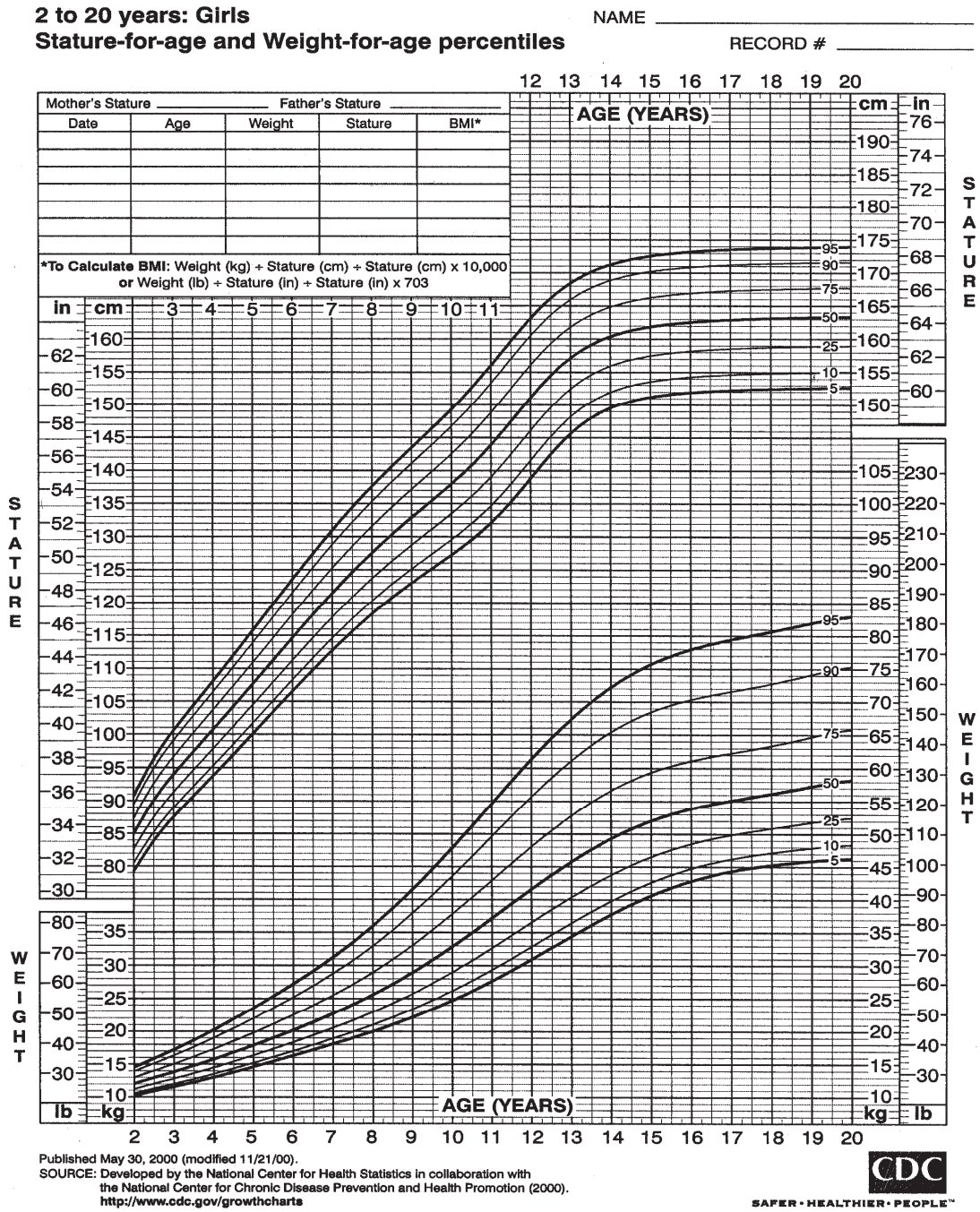
29. If you forget to take the drug or make a mistake with an injection, please call your study coordinator.

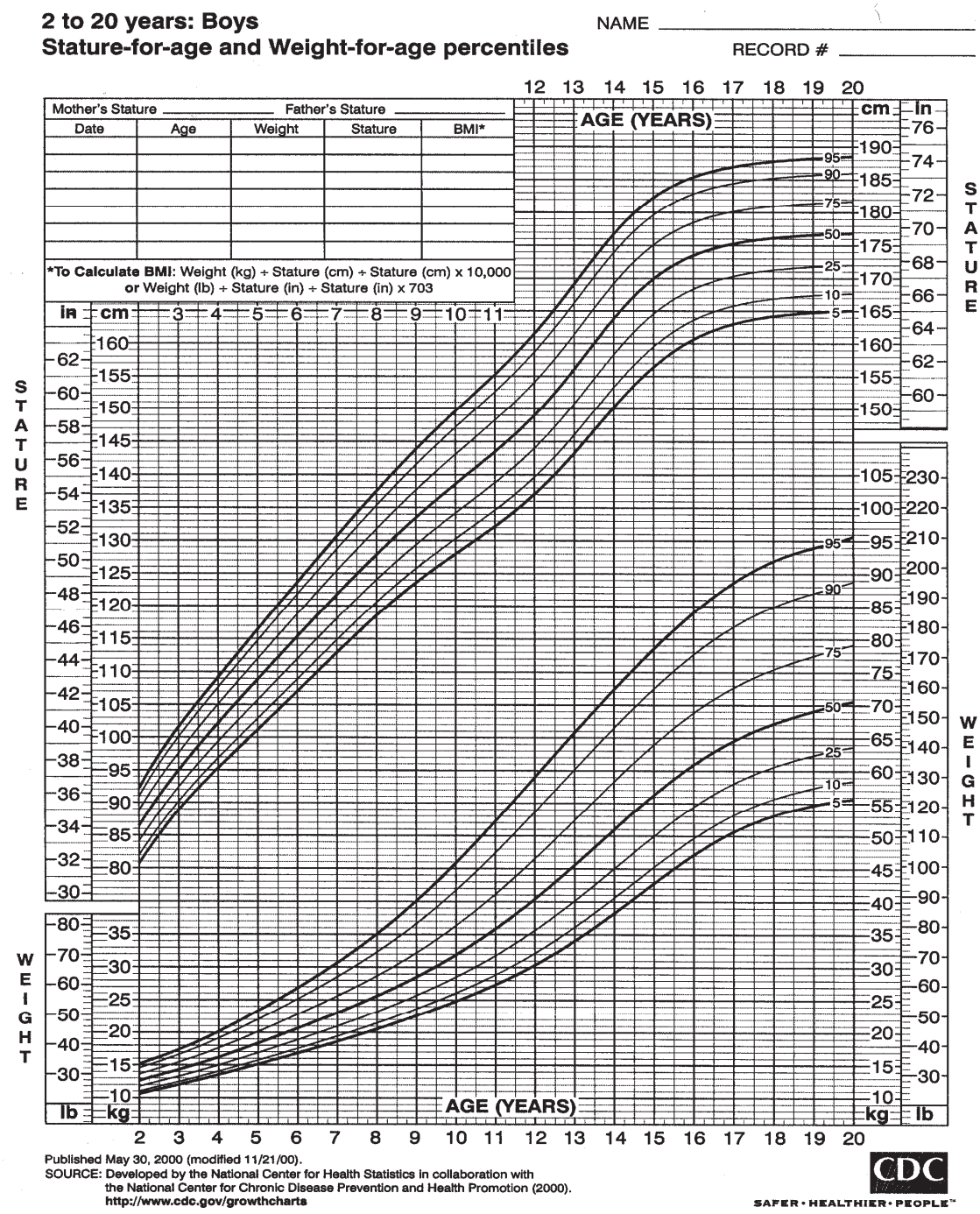
30. Please save all of your study medication, even if you skip a dose. Please bring all used and unused vials back to the physician at your next study visit.

31. There will be study medication remaining in the vials. DO NOT USE THE MEDICATION LEFT IN THE VIAL. Please return the vial along with the remaining study medication back to the physician at your next study visit.

32. Specific side effects to watch for: redness and swelling at the injection site. Please tell the study coordinator if you have any side effects from injecting the drug.

Appendix R. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER · HEALTHIER · PEOPLE™

Appendix S. Subject Abbott Laboratories Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix T. Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) - Caregiver

The following questions ask about the effect of your childs Crohns disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your childs Crohns disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your childs Crohns disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your childs Crohns disease affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your childs Crohns disease *affected your work only a little, choose a low number. Choose a high number if your childs* Crohns disease *affected your work a great deal.*

Consider only how much your childs Crohns disease affected your productivity <u>while you were working</u>.

My childs Crohns disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your childs Crohns Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your childs Crohns Disease affected your activities only a little, choose a low number. Choose a high number if your childs Crohns Disease affected your activities a great deal.

Consider only how much your childs Crohns disease affected your ability to do your regular daily activities, other than work at a job.

My childs Crohns disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:CD-Caregiver (US English)

Appendix U. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

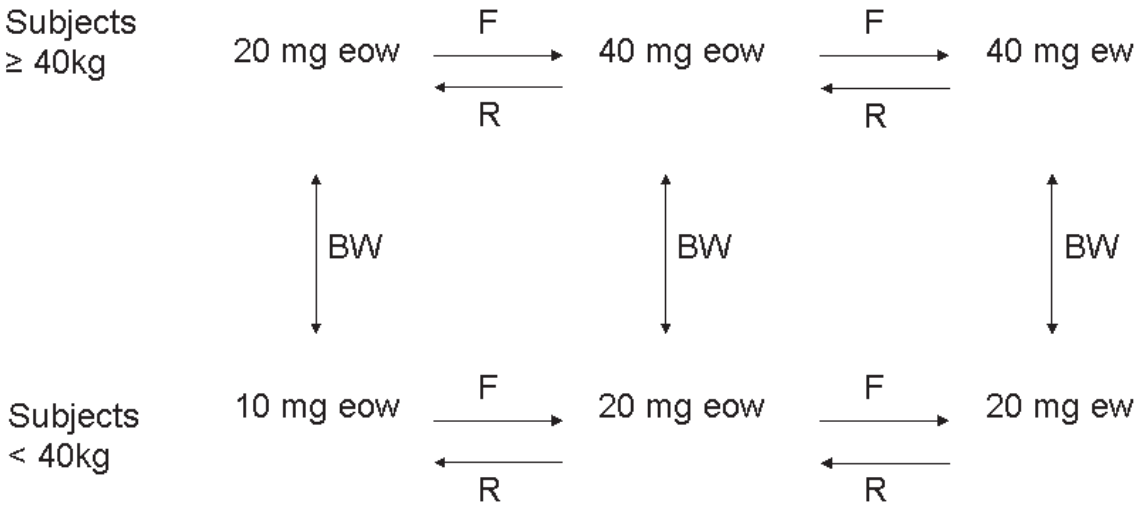
Section 5.1 Overall Study Design and Plan: Description
Fifteenth paragraph previously read:

A schematic of the study design is shown in Figure 1.

Has been changed to read:

A schematic of the study design is shown in Figure 1 (prior to Amendment 4) and in Figure 3 (after Amendment 4).

Figure 2. Dosing Schematic After Amendment 4
Add: new figure



F: Subjects who have a disease flare may be switched to the next higher treatment level.

R: Subjects who responded to their current treatment may be switched to the next lower treatment level at the discretion of the investigator after discussion with the medical monitor. Response is defined as a) a ≥ 15 points decrease in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) a ≥ 15 points decrease in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate.

BW: Subjects with an increase in body weight to ≥ 40 kg may increase their dose to the next higher level at the discretion of the investigator after discussion with the medical monitor. Subjects with a decrease in body weight to < 40 kg may decrease their dose to the next lower level at the discretion of the investigator after discussion with the medical monitor.

Table 1. Study Activities
Table note "l." previously read:

l. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

Has been changed to read:

l. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

Section 5.5.1 Treatments Administered
First paragraph previously read:

All study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL.

Has been changed to read:

Study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL or in vials containing adalimumab 40 mg/0.8mL.

Section 5.5.1 Treatments Administered
Add: new sixth, seventh, eighth and ninth paragraph

The dose of adalimumab may be decreased to the next lower treatment level as applicable, at the discretion of the Investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subject's body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as (a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who

dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

Section 5.5.2 Identity of Investigational Product
First paragraph, second sentence previously read:

Pre-filled syringes will be provided for this open-label clinical study.

Has been changed to read:

Pre-filled syringes (used for 40 mg/0.8 mL or 20 mg/0.4 mL doses) and 40 mg/0.8 mL vials (used for 10 mg dose) will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products
Previously read:

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

Has been changed to read:

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott
Adalimumab	40 mg/0.8 mL (used for 10 mg dose) Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

Section 5.5.2.1 Packaging and Labeling
Second paragraph previously read:

The following information will appear on the pre-filled syringe or carton labels:

Has been changed to read:

The following information will appear on the pre-filled syringe, vial or carton labels:

Section 5.5.2.1 Packaging and Labeling
First paragraph previously read:

Two pre-filled syringes will be provided in a dosing kit carton (see Table 4).

Has been changed to read:

Two pre-filled syringes or vials will be provided in a dosing kit carton (see Table 4).

Table 4. Study Drug Packaging and Administration
Previously read:

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.

Has been changed to read:

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.
Open-label Vials (used for 10 mg dose)	
Open-label kit cartons containing two vials of adalimumab 40 mg/0.8 mL.	

Section 5.5.2.2 Storage and Disposition of Study Drug
First paragraph, first sentence previously read:

Pre-filled syringes are to be stored protected from light at 2° to 8°C/ 36° to 46°F.

Has been changed to read:

Pre-filled syringes and vials are to be stored protected from light at 2° to 8°C/36° to 46°F.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Add: new fourth, fifth, sixth, and seventh paragraph

The dose of adalimumab may be decreased to the next lower treatment level as applicable at the discretion of the investigator and prior approval from the medical monitor, for subjects whose body weight has decreased from ≥ 40 kg to < 40 kg from the previous visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

Subjects who responded to treatment defined as a) an improvement of at least 15 points in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) an improvement of at least 15 points in PCDAI compared to Baseline of Study M06-806 in patients who did not dose-escalate) may have their dosage frequency decreased from ew to eow dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to the dose frequency decrease. At least 8 weeks after dose frequency decrease, subjects who still responded to treatment (as defined above) may have their dosage decreased (subjects who weigh ≥ 40 kg will receive 20 mg eow of adalimumab, while subjects who weigh < 40 kg

will receive 10 mg eow of adalimumab). The investigator should receive prior approval from the medical monitor before taking any action with regard to dose decrease.

Subjects who experience a disease flare may re-increase their dosage or dose frequency to the next higher treatment level regardless of prior dose or dose frequency decrease.

Simultaneous dose adjustment based on change of body weight as well as based on diseases status (response/flare) is prohibited.

Section 5.5.6 Treatment Compliance
Second paragraph previously read:

In order to document compliance with the treatment regimen, all pre-filled syringes will be counted and documented in source documents and on the appropriate drug accountability form.

Has been changed to read:

In order to document compliance with the treatment regimen, all pre-filled syringes and vials will be counted and documented in source documents and on the appropriate drug accountability form.

Section 5.5.7 Drug Accountability
First paragraph, fourth sentence previously read:

An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes dispensed, and the date study drug was dispensed for each subject.

Has been changed to read:

An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes or vials dispensed, and the date study drug was dispensed for each subject.

Section 5.5.7 Drug Accountability
First paragraph, sixth sentence previously read:

All unused pre-filled syringes will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories.

Has been changed to read:

All unused pre-filled syringes and vials will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories.

Section 5.5.7 Drug Accountability
Second paragraph previously read:

All used (expelled) pre-filled syringes will be inventoried by the site and verified by the CRA. The used syringes will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal container to store expelled syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes have been destroyed.

Has been changed to read:

All used (expelled) pre-filled syringes and vials will be inventoried by the site and verified by the CRA. The used syringes and vials will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit or vials boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal container to store expelled/used syringes.

Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes and used vials have been destroyed.

Section 5.6.4 Selection of Doses in the Study
Previously read:

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD. A model based on the JRA population was chosen because the body weight range will closely parallel that in a juvenile CD population. Escalation to weekly dosing will provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

Has been changed to read:

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 before Amendment 4 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD before Amendment 4. A model based

on the JRA population was chosen because the body weight range would closely parallel that in a juvenile CD population. Escalation to weekly dosing would provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provides investigators with the option of dose de-escalation by reducing the dose or switching from ew to eow based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients will have the option to be switched to this dose based on their body weight and clinical status at the discretion of the investigator.

Section 8.1.1 Analyzable Population
Delete: second sentence

In order to evaluate the impact of major protocol violations / deviations on the results of the study, additional analyses may be performed on the per-protocol population, which excludes all subjects with major protocol deviations.

Section 8.1.2.2 Primary Efficacy Analysis
Section title previously read:

Primary Efficacy Analysis

Has been changed to read:

Efficacy Analysis

Section 8.1.3 Other Analyses
First paragraph previously read:

The primary endpoint will be analyzed for the following subgroups in the ITT population.

Has been changed to read:

Efficacy will be analyzed for the following subgroups in the ITT population.

Section 8.1.4 Safety Analyses
First paragraph, second sentence previously read:

Treatment-emergent, and post−treatment AEs will be summarized.

Has been changed to read:

Treatment-emergent AEs will be summarized.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Clinical
		Clinical

Appendix F. Non-Drug Materials Provided to the Study Site(s)
Add: new ninth item following first paragraph

Dosing syringes, as applicable

Appendix Q. Self Injection Instructions
Previously read:

Has been changed to read:

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

For 40 mg dose, one pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 20 mg dose, one pre-filled syringe will contain 0.4 mL of liquid. The total available dose is 0.4 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

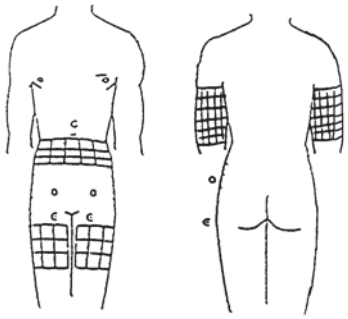
Remember to complete your dosing diary after each injection and to call the doctors office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

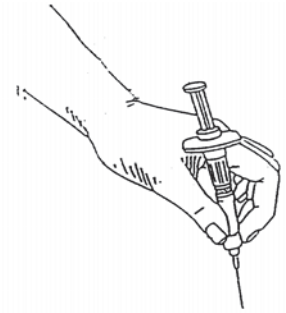
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



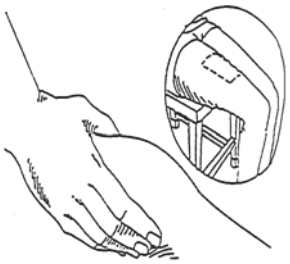
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

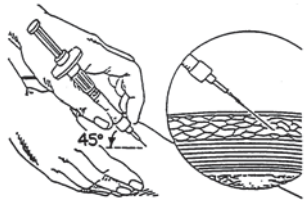


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

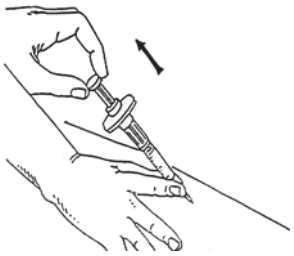
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

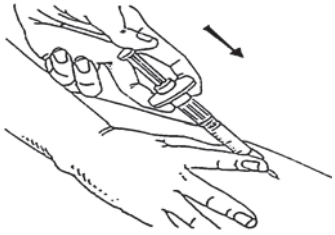


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



11. Remove needle while maintaining a 45-degree angle.

12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Self Injection Instructions

Subject Instructions

0.2 mL dose

Vials

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Vials**

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

The injection for the visits at Weeks 4, 8, 12, 16, 20, 26, 32, 40, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 10, 14 etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

The total dose is 0.2 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

For 10 mg dose, 0.2 mL of the solution is drawn from a vial containing adalimumab 40 mg/0.8 mL solution. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused vials to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused vials should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information **Vials**

- Vials will be labeled "adalimumab."
- Store all adalimumab vials in your refrigerator NOT in the freezer. Should the vials accidentally become frozen, call your study coordinator.
- 0.2 mL = 0.2 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW VIAL EVERY INJECTION DAY.** There will be medication left in the vial. **DO NOT RE-USE.**
- Save all study drugs. ***Vials (used and unused) must be returned to the study center at each visit.*** Used vials and syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

Injection Instructions **Vials**

Select a clean, well-lit, flat surface.

1. Wash your hands thoroughly with soap and warm water. It is important to keep your work surface as clean as possible.

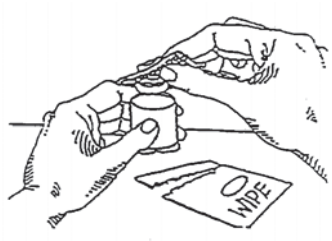
2. Open carton.

3. Examine the carton and components in it to make sure they are complete.

   - One or two vials containing adalimumab

4. Remove the plastic cap from the vial.

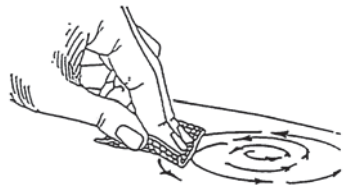
5. Wipe the gray stopper with an alcohol swab and discard alcohol swab.



6. Place the vial upright on a hard, flat surface.

7. Choose an injection site on the upper thigh or abdomen.

8. Prepare the injection site by wiping it thoroughly with a second alcohol swab. Use a circular motion.



9. Remove the needle cover from the syringe. *(The needle is sterile, so be very careful not to touch the needle or allow it to touch any surface.)*

10. Draw the plunger on the syringe back.

11. With the vial sitting on a hard, flat surface, insert needle straight down through the center of the gray stopper. If the needle is correctly lined up, you should feel slight resistance and then a "pop" as the needle penetrates the center of the stopper. (*Be careful not to insert the needle at an angle as this may cause the needle to bend. If the needle is not correctly aligned, you will feel constant resistance as it penetrates the stopper and will not feel a "pop.")*

12. Push the plunger in forcing air into the vial.

13. With the needle still in place, turn the vial upside down. Keeping the vial at eye level, slowly pull the plunger back to draw the liquid into the syringe. This will cause the bubbles to rise to the top of the syringe. *(As the liquid level in the vial drops, you may have to withdraw the needle partially to keep the tip of the needle in the liquid.)* Only 0.2 mL of the vial will be drawn into the syringe.

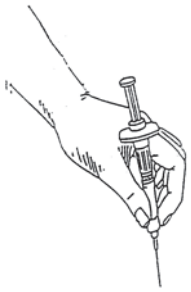
14. With the needle still in the vial, check the syringe for air bubbles. To remove any air bubbles, start by gently tapping the syringe.

15. Slowly press the plunger to push any bubbles out of the syringe and into the vial. *(If you accidentally push any liquid back into the vial, draw the liquid back into the syringe and check again for air bubbles. It's okay for a small amount of liquid to remain in the vial.)*

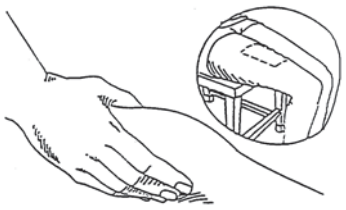
16. Withdraw the needle from the vial, being careful not to touch it to any surface.

Vials

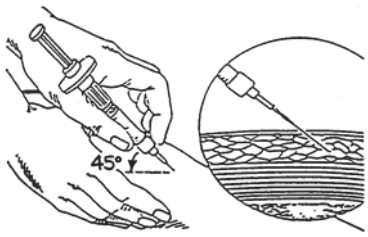
17. Take the syringe in one hand.



18. With your other hand, firmly pinch the skin around the cleaned injection site. *(Be careful not to touch the cleaned area.)*



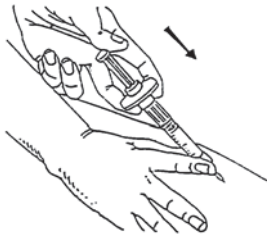
19. Hold the syringe at about a 45-degree angle to the skin and use a quick, short motion to push the needle into the skin.



20. Once the needle is in, release the skin.

Vials

21. While firmly holding the syringe with one hand, use your other hand to slowly push the plunger and inject the adalimumab. For subjects that weigh ≥ 40 kg, all 0.8 mL will be injected. For subjects that weigh < 40 kg, only 0.4 mL of the vial will be inject.



22. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same 45-degree angle.

23. Dispose of both the needle and syringe in a puncture-resistant container, or sharps container, which will be provided.

24. You may want to press a cotton ball on the injection site for 10 seconds. If there is some slight bleeding, you may choose to apply a small bandage.

25. Return the vial into the original packaging.

26. Place the medication kit back into the refrigerator.

Vials

EACH TIME YOU RECEIVE AN INJECTION OF STUDY MEDICATION, REMEMBER TO RECORD THE INFORMATION ON YOUR DOSING SHEET.

GENERAL INFORMATION:

27. ROTATING INJECTION SITES IS RECOMMENDED. PLEASE DO NOT INJECT THE STUDY MEDICATION INTO A PRIOR SITE OF INJECTION.

28. Store all of your drug in the refrigerator. Should the vials become accidentally frozen or left out, call your study coordinator. DO NOT USE THESE VIALS.

29. If you forget to take the drug or make a mistake with an injection, please call your study coordinator.

30. Please save all of your study medication, even if you skip a dose. Please bring all used and unused vials back to the physician at your next study visit.

31. There will be study medication remaining in the vials. DO NOT USE THE MEDICATION LEFT IN THE VIAL. Please return the vial along with the remaining study medication back to the physician at your next study visit.

32. Specific side effects to watch for: redness and swelling at the injection site. Please tell the study coordinator if you have any side effects from injecting the drug.

Document Approval

Study M06807 - 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 Crohns Disease Who Have Demonstrated a Clinical Response in the M06-806 Study - Amendment 4 - EudraCT 2007-006494-90 - 29Jun2011

Version: 1.0 **Date:** 30-Jun-2011 06:27:25 PM **Abbott ID:** 06302011-00AB619FF91D96-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	29-Jun-2011 05:04:02 PM	Author
	29-Jun-2011 06:29:27 PM	Approver
	30-Jun-2011 08:26:44 AM	Approver
	30-Jun-2011 06:27:25 PM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2, Amendment 1, Administrative Changes 3, 4, 5 and 6, and Amendments 2 and 3

Abbott Number / Investigational Product:	Adalimumab
Date:	14 December 2010
Development Phase:	3
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.
EudraCT Number:	2007-006494-90
Investigator:	Multicenter (Investigator information on file at Abbott Laboratories).
Sponsor:	European Union Countries: Abbott GmbH & Co.KG Knollstrasse 50 67061 Ludwigshafen, Germany Non European Union Countries: Abbott Laboratories, US 100 Abbott Park Road Abbott Park, IL 60064
Emergency Contact:	[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Include interim analysis.
- Clarify that the x-ray for bone age will not be performed at the unscheduled visit.
- Add a statement allowing the investigator to omit the x-ray for bone age and the determination of serum bone markers if the subject is no longer growing.
- Correct typographical errors.

An itemized list of all changes made to the protocol under this amendment can be found in Appendix U.

2.0 Table of Contents

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3.0 Introduction

Crohns Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is

heterogeneous with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohns disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohns disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and

133 subjects continued in a 32-week double blind segment. Clinically significant improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigators Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease. The subject

population will consist of subjects who participated in and successfully completed the M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigators discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigators discretion. For a detailed description of the study please see Section 5.0.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohns disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a

responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare is defined as an increase in the Pediatric Crohns Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI score obtained at the subjects previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohns treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohns specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 264 weeks (approximately 5 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohns Disease.
- All applicable local reimbursement procedures are completed.

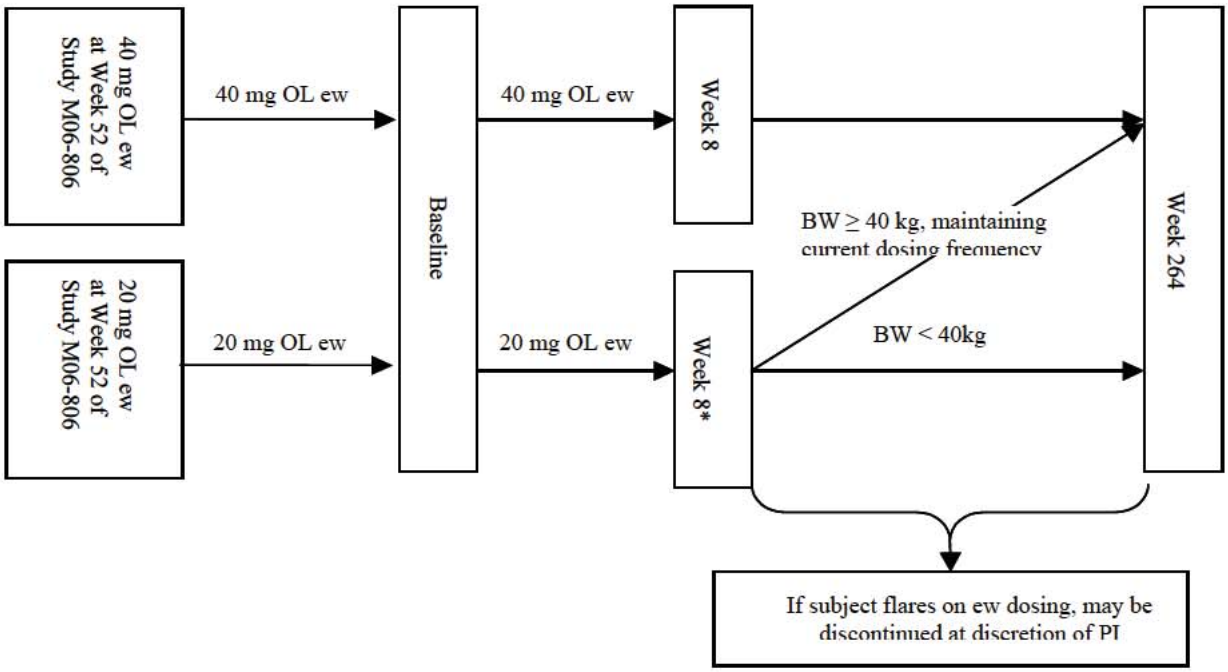
Sites will be notified once these criteria are met.

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

A schematic of the study design is shown in Figure 1.

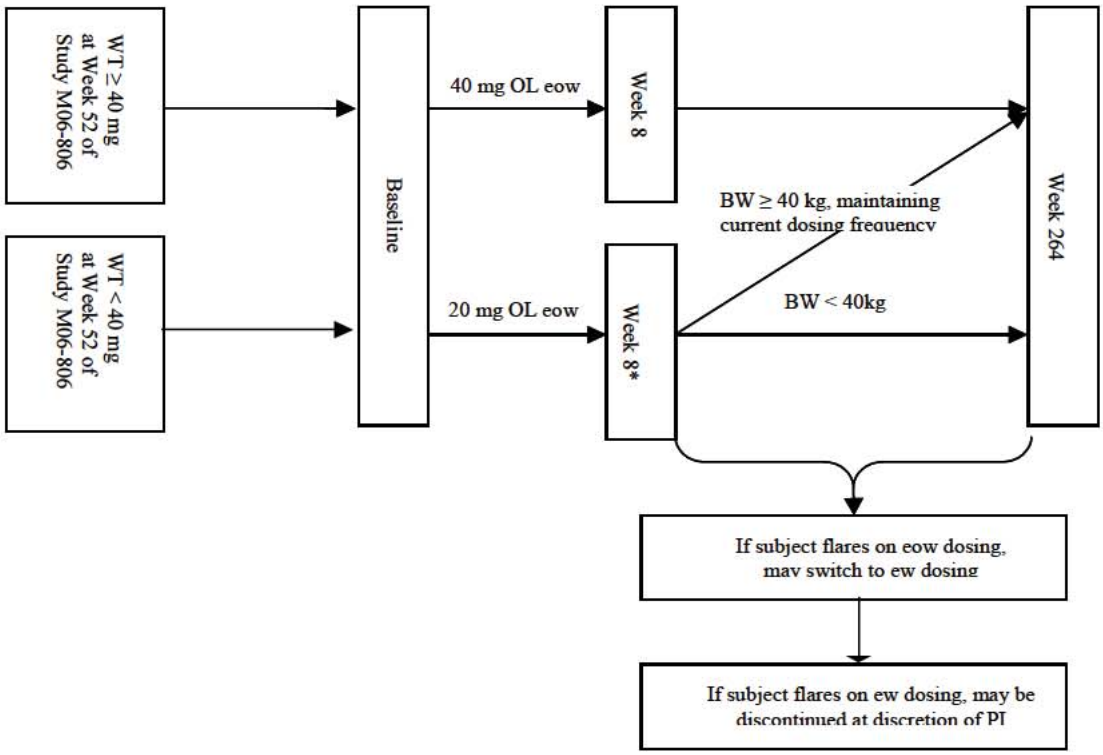
Figure 1. Study Schematic

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subjects parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subjects diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohns disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma−in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the

opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the Abbott Laboratories Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the Abbott Laboratories Medical Monitor identified in Section 7.0

5.2.3.2 Concomitant Therapy

Adjustments of Crohns related concomitant treatments, including Crohns related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohns related antibiotics or Crohns related concomitant treatments are allowed according to the Investigators medical judgment. These adjustments may be performed without prior discussion with the Abbott Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohns related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and Subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg ≤ 10 mg	5 mg/week 2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix L).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample[j]					X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age[i]			X				X						X		
Serum bone markers[i]	X		X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[l]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264/ET and unscheduled visits.
i. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.
j. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
k. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
l. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228 and 252 in order to collect any safety information from the subject as illustrated in Table 1.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institutions IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of

legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 264/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subjects casebook from the previous study (M06-806). They will not be required to be captured in the subjects casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subjects M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix O) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the sites local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured as indicated in Table 1. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohns Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix G. Instructions for completing the PCDAI score is located in Appendix H.

Crohns Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix H.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix I.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1. A copy of the questionnaire is located in Appendix K.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix N, Appendix T).

The subjects parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x−ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by Abbott Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr) / SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Week 264/ET visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s)

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix M for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subjects home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study

drug administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix P.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/- 3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/- 3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06−806).

5.3.2 Drug Concentration Measurements

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collected prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

5.3.2.1 Collection of Samples for Analysis

Collection of Samples for Adalimumab Analysis

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 blood samples are planned to be collected per subject for AAA analysis.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the

assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a −20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

5.3.2.3 Disposition of Samples

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither Abbott nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

5.3.5 Pharmacokinetic Variables

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subjects legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non−melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 264/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subjects condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigators best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

Abbott reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

5.5 Treatments

5.5.1 Treatments Administered

All study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subjects body weight into the IVRS and the dose will be adjusted, if applicable.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

5.5.2.1 Packaging and Labeling

The following information will appear on the pre-filled syringe or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of Administration
- Excipients
- Blank spaces to write the subjects identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes are to be stored protected from light at 2° to 8°C/ 36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until Abbott GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to Abbott Laboratories.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call−in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06−806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix P).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix S. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes will be inventoried by the site and verified by the CRA. The used syringes will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit boxes, subject diaries and by visually counting the syringes in the sharps container whenever possible. Used sharps containers should never be opened. Each subject will be given their own sharps disposal

container to store expelled syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohns disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from

pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD. A model based on the JRA population was chosen because the body weight range will closely parallel that in a juvenile CD population. Escalation to weekly dosing will provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Abbott as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subjects hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subjects usual activities.
Severe	The AE causes considerable interference with the subjects usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.

Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

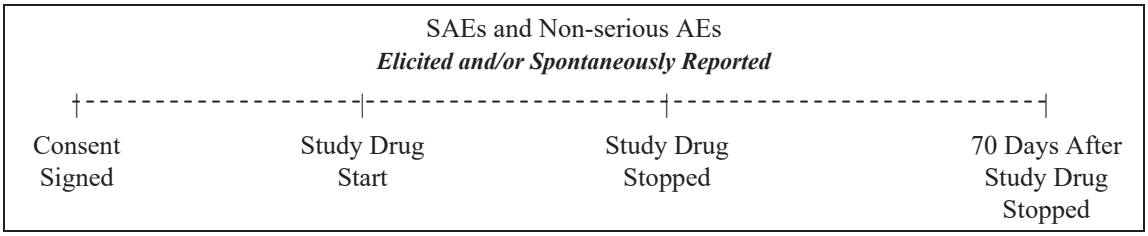
If an Investigators opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

For all sites:

[redacted]

For questions regarding SAEs, please contact:

[redacted]

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohns disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Abbott Laboratories must be notified within 1 working day of a sites learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a study subject will be collected. Upon notification of a pregnancy Abbott will forward a form to the site, for the Investigator to complete and send back to Abbott. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to Abbott.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States, Canada and Puerto Rico. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott representative:

[redacted]

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by Abbott to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. In order to evaluate the impact of major protocol violations / deviations on the results of the study, additional analyses may be performed on the per-protocol population, which excludes all subjects with major protocol deviations. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation,

mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind study M06-806).

8.1.2.2 Primary Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subjects last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

The primary endpoint will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]
- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent, and post−treatment AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and

system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be provided to cross-classify and tabulate subjects value from baseline to final value by the presence of clinically significant laboratory results. Each subjects baseline value and final value will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.4.1 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

8.1.5 Interim Analysis

There will be one planned interim analysis. Details of the analysis will be described in the study SAP.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigators Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix C.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to Abbott.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institutions IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subjects parent/legal guardian. The original signed ICF and Assent Form will be placed in the

subjects medical record. An entry must also be made in the subjects dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subjects source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by Abbott. These forms will be used to transmit information collected during the study to Abbott and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case

report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by Abbott personnel (or their representatives). Abbott (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by Abbott. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigators meeting will be held with Abbott personnel, the Investigators and their study coordinators, the CROs project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigators meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality

assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All data hand entered in the database will be verified by a double-key entry procedure at Abbott. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

Sites will provide Abbott (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and Abbott Laboratories operations, such as Abbott Laboratories patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of adalimumab. This information may be disclosed as deemed necessary by Abbott Laboratories to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by Abbott.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and Abbott. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and Abbott. The Investigator will provide a summary of the studys outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to Abbott or their designee.

Abbott may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Abbott terminates the study for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Abbott will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigators Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subjects last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigators Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title: 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

Protocol Date: 14 December 2010

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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2. Loftus Jr. EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504-17.

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohns disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form

IRB	Institutional Review Board
ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N−telopeptide
OL	Open-Label
PCDAI	Pediatric Crohns Disease Activity Index
PK	Pharmacokinetics
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohns Disease

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Clinical
		Clinical

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigators agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigators agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigators agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institutions General Assurance Number.

- If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union

Appendix D. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigators qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigators Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix E. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

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Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix F. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Appendix G. Pediatric Crohns Disease Activity Index (PCDAI)

							Score
1.	Abdominal pain rating						
	- None		= 0 p				
	- Mild - Brief, does not interfere with activities		= 5 p				
	- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p				
2.	Stools (per day)						
	- 0–1 liquid stools, no blood		= 0 p				
	- Up to 2 semi-formed with small blood, or 2–5 liquid		= 5 p				
	- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p				
3.	Patient Functioning, General Well-Being						
	- No limitation of activities, well		= 0 p				
	- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p				
	- Frequent limitation of activity, very poor		= 10 p				
LABORATORY							**Score**
4.	HCT: Male and female ≤ 10 years:			Male 11–14 years:			
		≥ 33	= 0 p		≥35	= 0 p	
		28-32	= 2.5 p		30-34	= 2.5 p	
		< 28	= 5 p		<30	= 5 p	
	Female 11–19 years:	≥ 34	= 0 p	Male 15–19 years:	≥37	= 0 p	
		29-33	= 2.5 p		32-36	= 2.5 p	
		< 29	= 5 p		<32	= 5 p	
5.	ESR (mm/hr)	< 20	= 0 p				
		20-50	= 2.5 p				
		> 50	= 5 p				
6.	Albumin (g/dL)	≥ 3.5	= 0 p				
		3.1-3.4	= 5 p				
		≤ 3.0	= 10 p				

EXAMINATION			**Score**
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥ 10%	= 10 p	
8. Height	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations (Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)			
	- None	= 0 p	
	- One	= 5 p	
	- ≥ Two	= 10 p	
TOTAL SCORE	**Pediatric Crohns Disease Activity Index (PCDAI)**		

Appendix H. PCDAI Users Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohns disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohns disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 264: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48
- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216

The intent is to assess the normalcy vs. impairment of the subjects recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

$$\frac{\text{Present height} - \text{Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

    a. Velocity less than "Minus 2 SD" scores 10 points.

    b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

    c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	Minus 2SD	Minus 1SD	Mean
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix I. Crohns Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0=none, 1=mild, 2=moderate, 3=severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0=generally well, 1=slightly underpar, 2=poor, 3=very poor, 4=terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil / Imodium / Loperamide /opiates for diarrhea 0=no, 1=yes	_____	X	30	
6. Abdominal mass 0=none, 2=questionable, 5=defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix J. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. Add item requested for each day.	Crohns Disease Activity Index Subject Diary Card						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0=none, 1=mild, 2=moderate, 3=severe)							
Daily rating of general well being. (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)							

Subject Initials:_____ Subjects Signature:_____

Investigator or Designees Signature:_____

Appendix K. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohns disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I dont feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I dont think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I dont try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I dont feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix L. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix M. Day 70 Phone Call

Site Name / Number: _____

Subject Number:_____

Subject Initials:_____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to Abbott within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted]

Appendix N. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohns disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohns Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix O. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctors office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix P. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctors office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctors office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13- Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263*					

* Week 263 dose will only be taken if on every-week dosing schedule.

Appendix Q. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctors office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

One pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

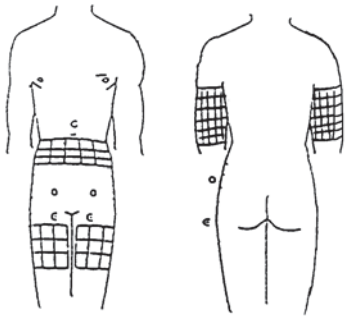
Remember to complete your dosing diary after each injection and to call the doctors office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

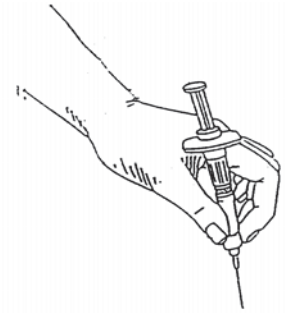
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



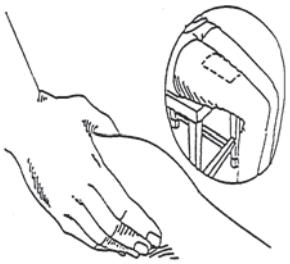
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

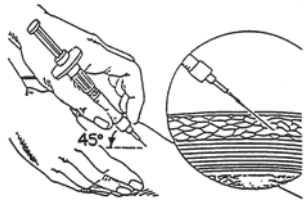


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

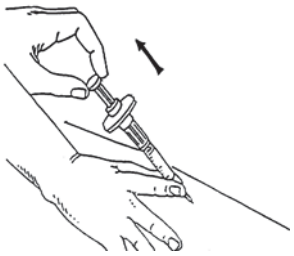
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

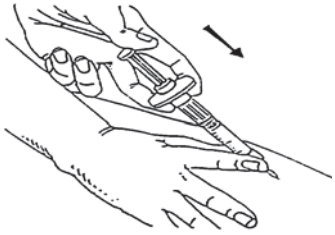


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



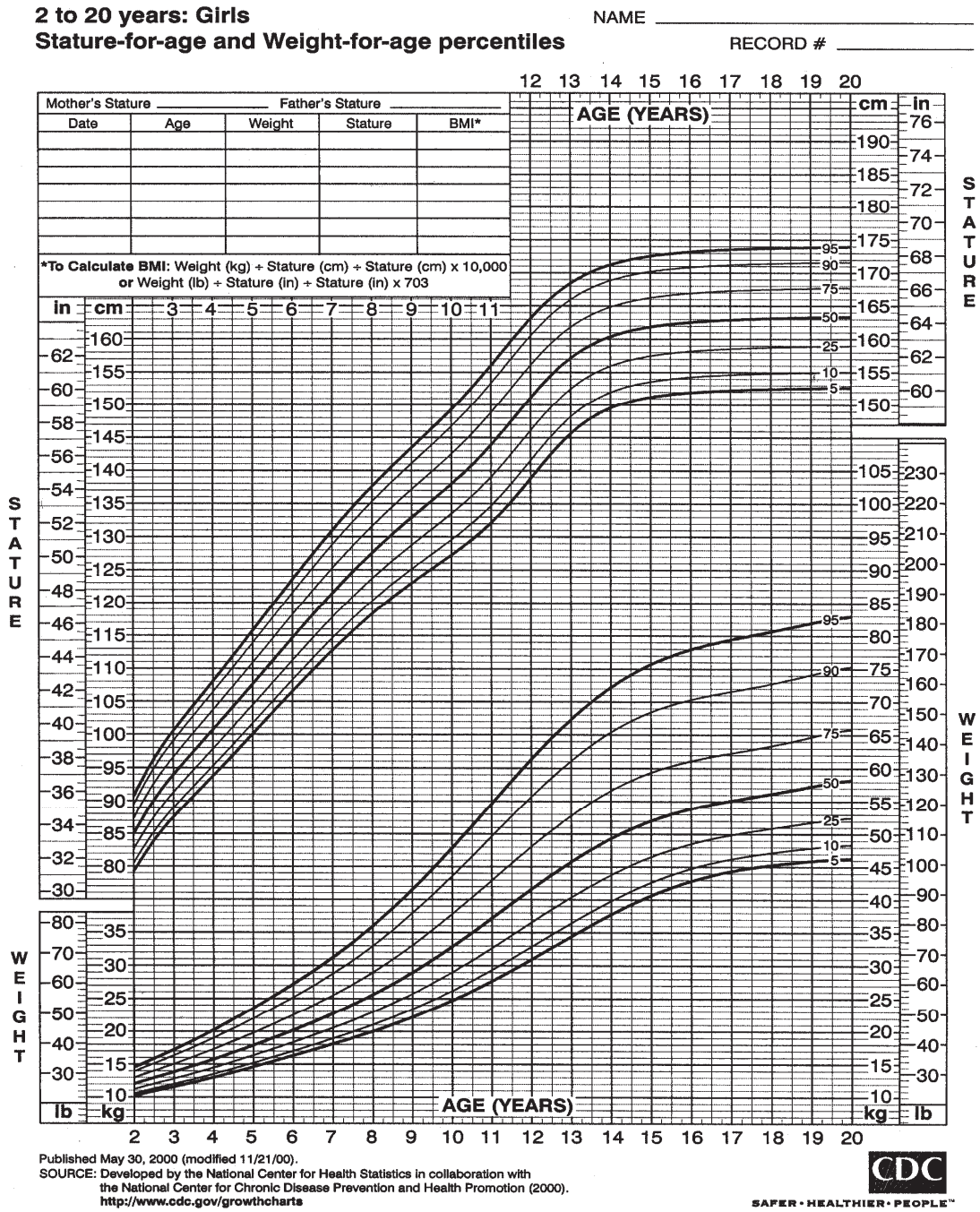
11. Remove needle while maintaining a 45-degree angle.

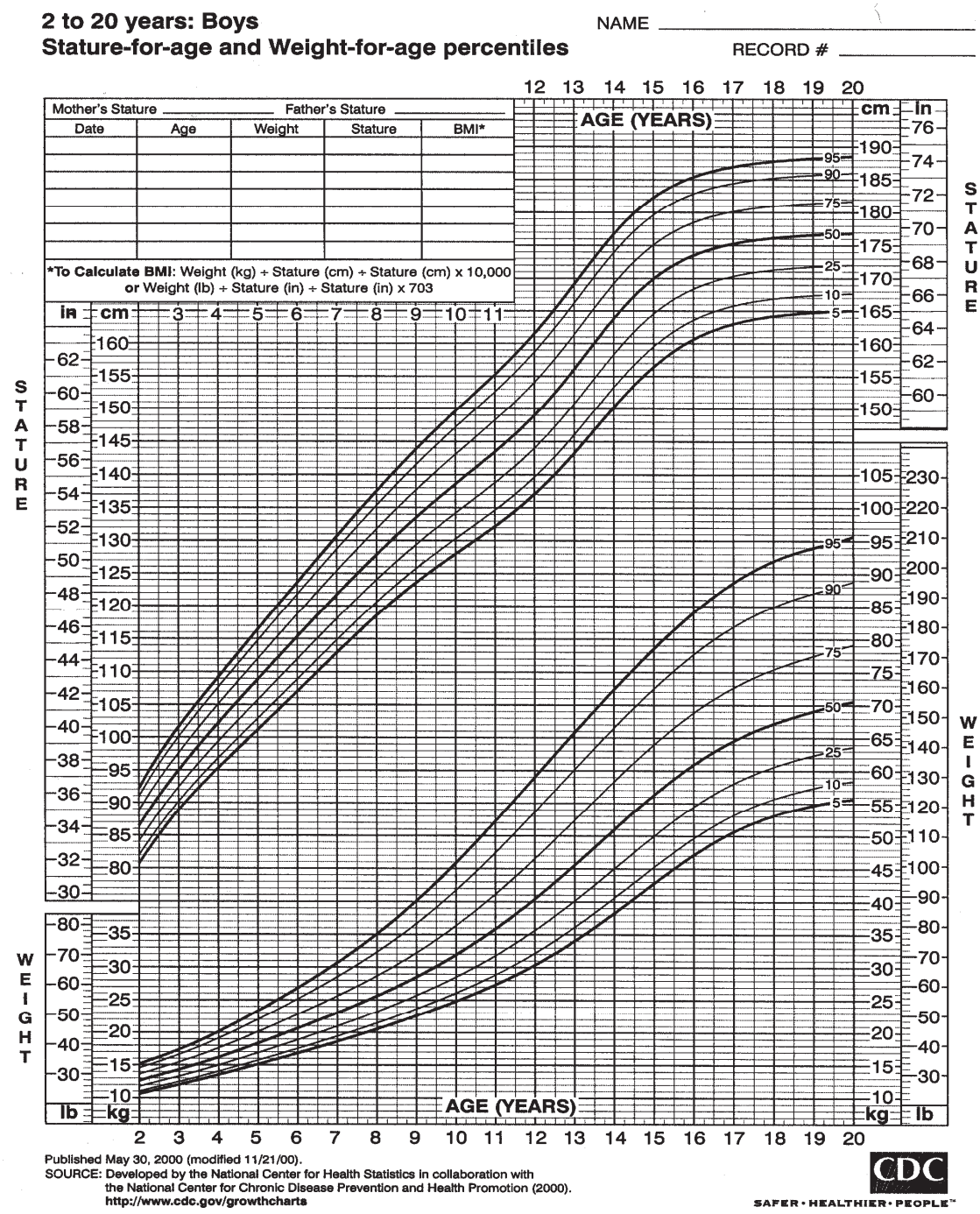
12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Appendix R. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER · HEALTHIER · PEOPLE™

Appendix S. Subject Abbott Laboratories Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix T. Work Productivity and Activity Impairment Questionnaire: Crohns Disease (WPAI-CD) - Caregiver

The following questions ask about the effect of your childs Crohns disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

---

2. During the past seven days, how many hours did you miss from work because of problems associated with your childs Crohns disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your childs Crohns disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your childs Crohns disease affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your childs Crohns disease *affected your work only a little, choose a low number. Choose a high number if your childs* Crohns disease *affected your work a great deal.*

Consider only how much your childs Crohns disease affected your productivity while you were working.

My childs Crohns disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your childs Crohns Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your childs Crohns Disease affected your activities only a little, choose a low number. Choose a high number if your childs Crohns Disease affected your activities a great deal.

Consider only how much your childs Crohns disease affected your ability to do your regular daily activities, other than work at a job.

My childs Crohns disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My childs Crohns disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

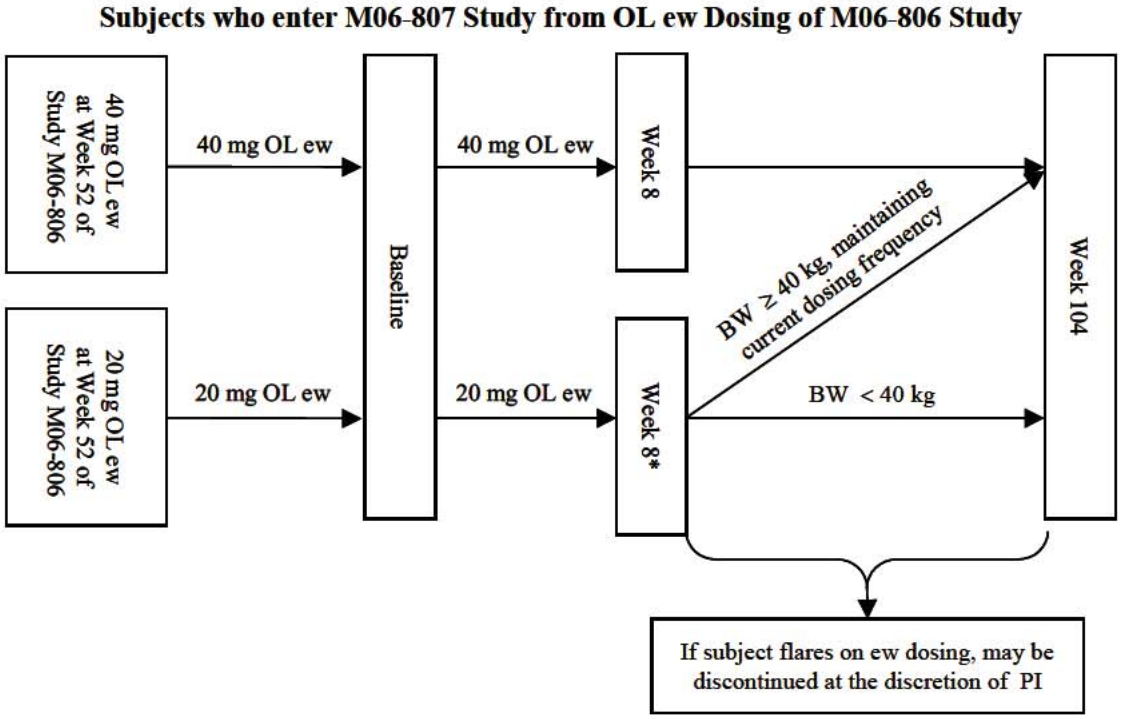
WPAI:CD-Caregiver (US English)

Appendix U. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

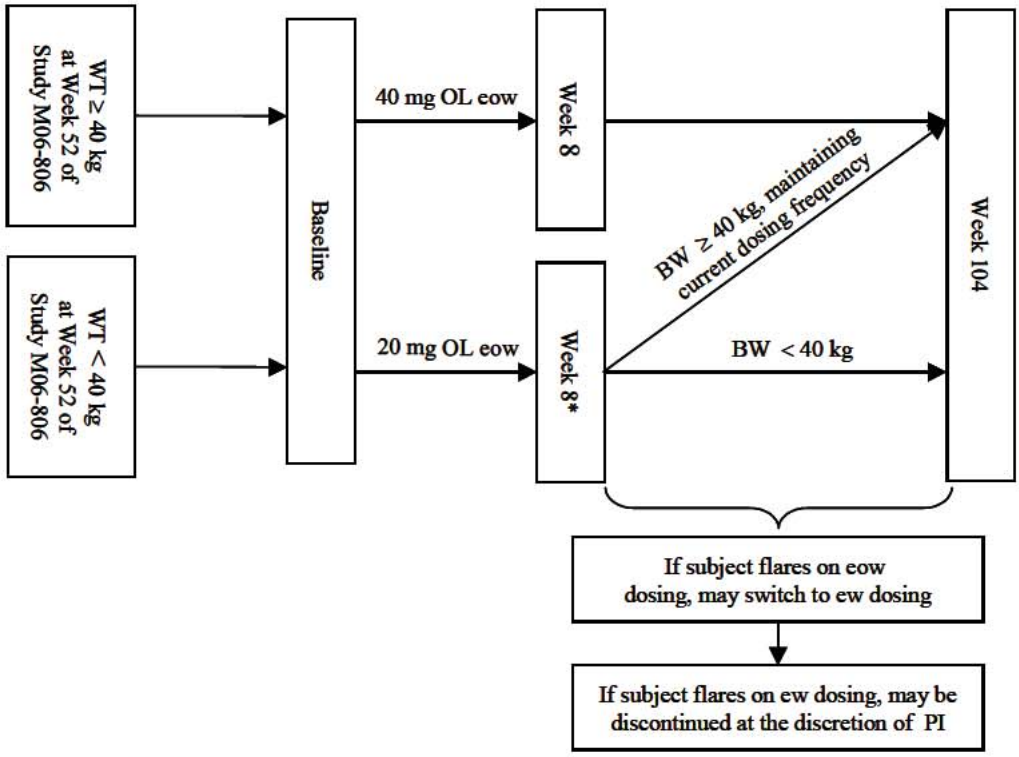
Specific Protocol Changes:

Figure 1. Study Schematic
Previously read:



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

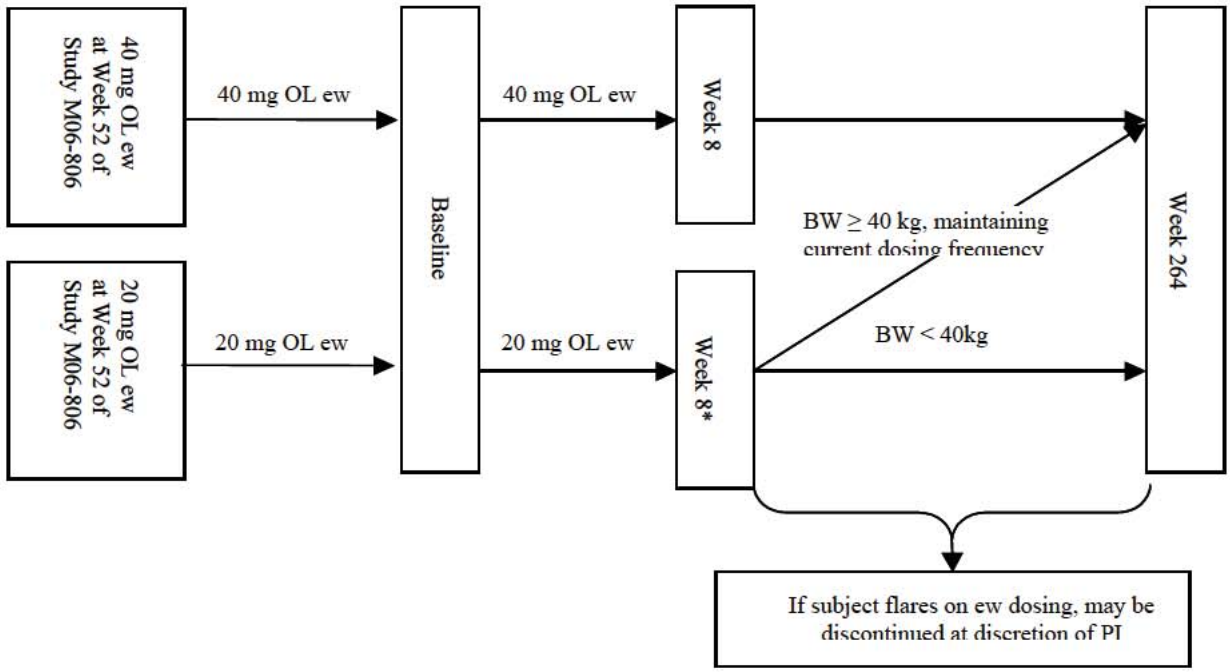
Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

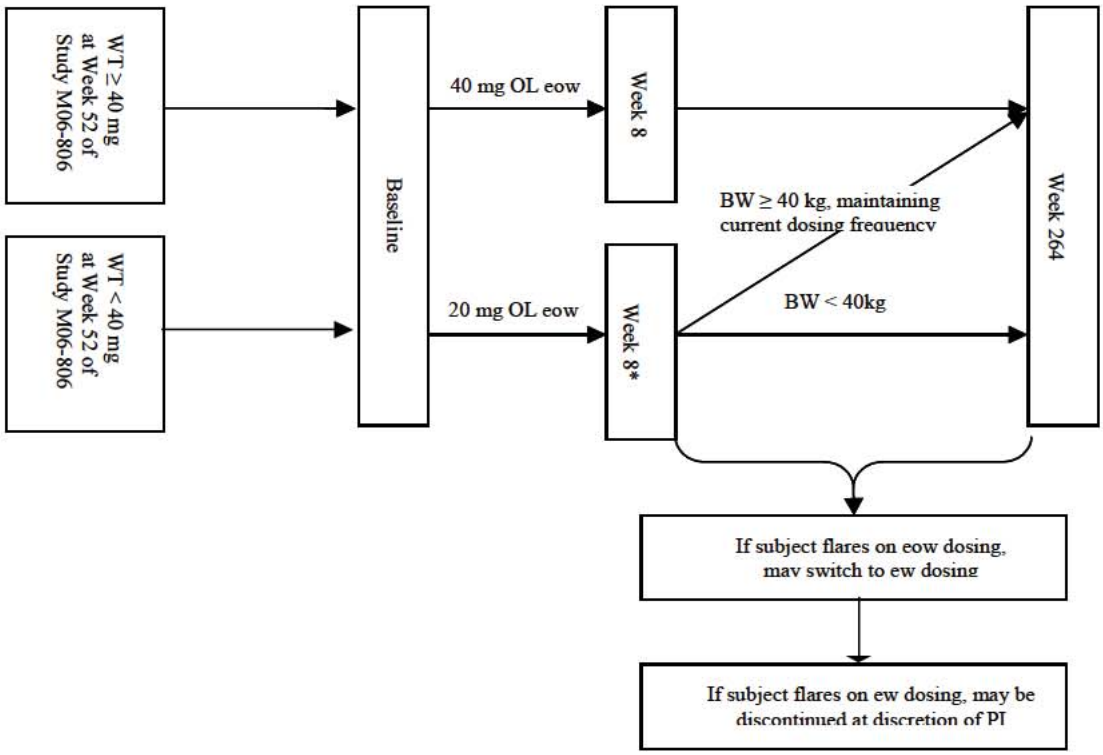
Has been changed to read:

Subjects who enter M06-807 Study from OL ew Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



*At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Table 1. Study Activities
Previously read:

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample					X		X		X		X	
Anti-adalimumab blood levels (AAA)					X		X		X		X	
Adverse events[i]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age			X				X						X	X	
Serum bone markers	X		X		X		X		X		X		X	X	
PK Blood Sample[i]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[i]	X		X		X		X		X		X		X	X	
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[k]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 144, 168, 192, 216, 240 and 264/ET.
i. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
j. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
k. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

Has been changed to read:

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age[i]	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample[j]					X		X		X		X	
Anti-adalimumab blood levels (AAA)[j]					X		X		X		X	
Adverse events[k]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohns Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age[i]			X				X						X		
Serum bone markers[i]	X		X		X		X		X		X		X	X	
PK Blood Sample[j]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[j]	X		X		X		X		X		X		X	X	
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[l]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264/ET and unscheduled visits.
i. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.
j. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
k. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
l. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

Section 5.3.2 Drug Concentration Measurements
First paragraph, fourth sentence previously read:

At each visit, blood samples will be collect prior to study drug administration at each visit.

Has been changed to read:

At each visit, blood samples will be collected prior to study drug administration at each visit.

Section 8.1.5 Interim Analysis
Previously read:

There are no planned interim analyses.

Has been changed to read:

There will be one planned interim analysis. Details of the analysis will be described in the study SAP.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical
		Clinical

Appendix P. Subject Dosing Diary
Diary "Week 241 - Week 263"
Footnote previously read:

* Week 259 dose will only be taken if on every-week dosing schedule.

Has been changed to read:

* Week 263 dose will only be taken if on every-week dosing schedule.

Document Approval

Study M06807 - 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 Crohns Disease Who Have Demonstrated a Clinical Response in the M06-806 Study - Amendment 3 - EudraCT 2007-006494-90 - 14Dec2010

Version: 1.0 **Date:** 17-Dec-2010 12:08:10 AM **Abbott ID:** 12172010-00AB619FE12E6B-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	14-Dec-2010 07:05:41 PM	Author
	14-Dec-2010 10:11:04 PM	Approver
	15-Dec-2010 10:27:18 AM	Approver
	17-Dec-2010 12:08:09 AM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2, Amendment 1, Administrative Changes 3, 4, 5 and 6, and Amendment 2

Abbott Number / Investigational Product:	Adalimumab
Date:	26 August 2010
Development Phase:	3
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.
EudraCT Number:	2007-006494-90
Investigator:	Multicenter (Investigator information on file at Abbott Laboratories).
Sponsor:	European Union Countries: Abbott GmbH & Co.KG Knollstrasse 50 67061 Ludwigshafen, Germany Non European Union Countries: Abbott Laboratories, US 100 Abbott Park Road Abbott Park, IL 60064
Emergency Contact:	[redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Add blood sample collections for adalimumab concentration and anti-adalimumab antibody (AAA) assays. PK and AAA was analyzed as part of Study M06-806. Additional PK and AAA collection from long-term treatment in these subjects will be used for further analysis of pharmacokinetic and safety data in pediatric CD patients.
- Change the stopping criteria for study based on discussion and recommendation by the DMC members. Stoppage of the study will be assessed at each meeting by the DMC but there will be no stringent criteria since the subjects are no longer blinded (due to completion of M06-806 study).
- Add subject visits through Week 264 and provision for study to continue until local regulatory approval. Extension of this open-label study is necessary to allow for continued collection of long-term safety and efficacy information on these pediatric CD subjects.
- Incorporate Administrative Changes 3 through 6 into this protocol.
- Added new required template for protocol signatories (Appendix B).

An itemized list of all changes made to the protocol under this amendment can be found in Appendix U.

2.0 Table of Contents

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3.0 Introduction

Crohn's Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is

heterogeneous with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohn's disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohn's disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and

133 subjects continued in a 32-week double blind segment. Clinically significant improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigator's Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease. The subject

population will consist of subjects who participated in and successfully completed the M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigator's discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigator's discretion. For a detailed description of the study please see Section 5.0.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a

responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare is 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 subject's previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects' body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohn's treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohn's specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 264 weeks (approximately 5 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

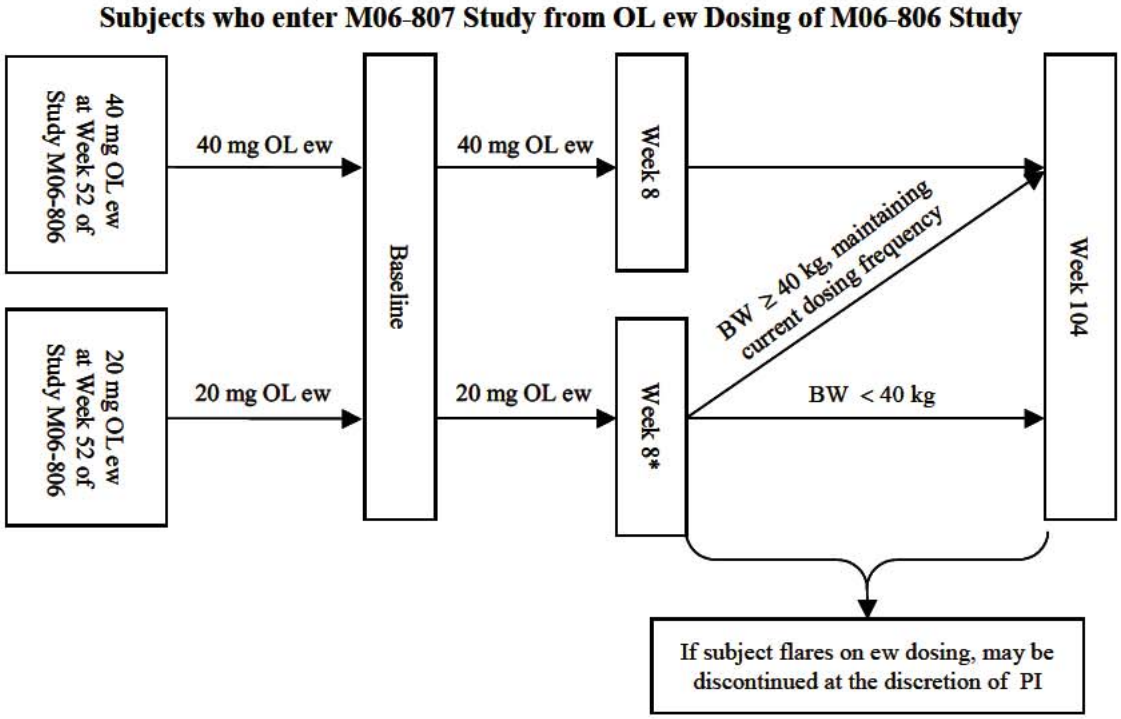
- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohn's Disease.
- All applicable local reimbursement procedures are completed.

Sites will be notified once these criteria are met.

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

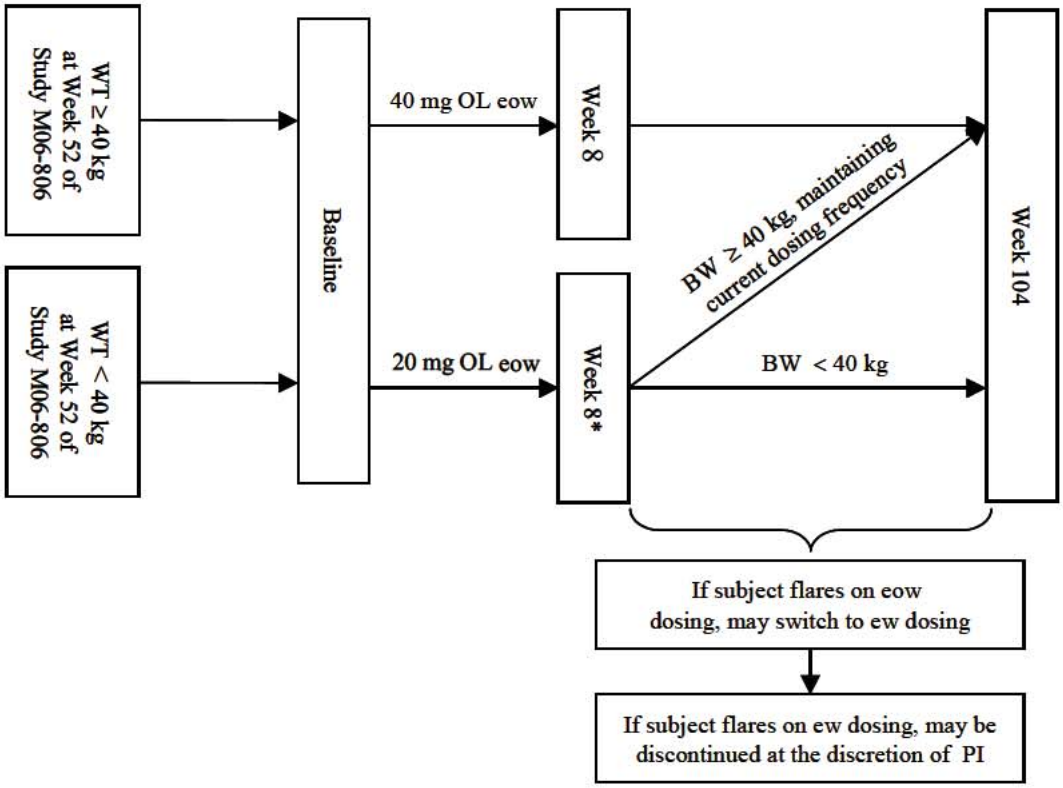
A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subject's parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subject's diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohn's disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma−in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the

opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the Abbott Laboratories Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the Abbott Laboratories Medical Monitor identified in Section 7.0

5.2.3.2 Concomitant Therapy

Adjustments of Crohn's related concomitant treatments, including Crohn's related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohn's related antibiotics or Crohn's related concomitant treatments are allowed according to the Investigator's medical judgment. These adjustments may be performed without prior discussion with the Abbott Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohn's related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and Subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg	5 mg/week
	≤ 10 mg	2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix L).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample					X		X		X		X	
Anti-adalimumab blood levels (AAA)					X		X		X		X	
Adverse events[i]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age			X				X						X	X	
Serum bone markers	X		X		X		X		X		X		X	X	
PK Blood Sample[i]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[i]	X		X		X		X		X		X		X	X	
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[k]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 144, 168, 192, 216, 240 and 264/ET.
i. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
j. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
k. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228 and 252 in order to collect any safety information from the subject as illustrated in Table 1.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institution's IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of

legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subject's source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 264/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subject's casebook from the previous study (M06-806). They will not be required to be captured in the subject's casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subject's M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix O) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the site's local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured as indicated in Table 1. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohn's Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix G. Instructions for completing the PCDAI score is located in Appendix H.

Crohn's Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix H.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix I.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1. A copy of the questionnaire is located in Appendix K.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix N, Appendix T).

The subject's parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x−ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by Abbott Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr) / SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through the Week 264/ET visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s)

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix M for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subject's home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study

drug administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix P.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/- 3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/- 3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06−806).

5.3.2 Drug Concentration Measurements

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collect prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

5.3.2.1 Collection of Samples for Analysis

Collection of Samples for Adalimumab Analysis

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 blood samples are planned to be collected per subject for AAA analysis.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the

assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a −20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

5.3.2.3 Disposition of Samples

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither Abbott nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

5.3.5 Pharmacokinetic Variables

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subject's legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non−melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 264/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

Abbott reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

5.5 Treatments

5.5.1 Treatments Administered

All study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

5.5.2.1 Packaging and Labeling

The following information will appear on the pre-filled syringe or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of Administration
- Excipients
- Blank spaces to write the subject's identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix Q.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes are to be stored protected from light at 2° to 8°C/ 36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until Abbott GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to Abbott Laboratories.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call−in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06−806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix P).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix S. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes will be inventoried by the site and verified by the CRA. The used syringes will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit boxes, subject diaries and by visually counting the syringes in the sharp's container whenever possible. Used sharp's containers should never be opened. Each subject will be given their own sharps

disposal container to store expelled syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohn's disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 was developed using an analogous approach as that studied in the adult CD population.

Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD. A model based on the JRA population was chosen because the body weight range will closely parallel that in a juvenile CD population. Escalation to weekly dosing will provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Abbott as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.

Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

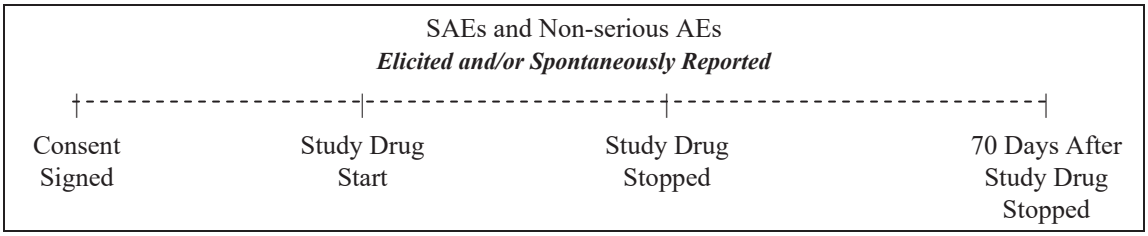
If an Investigator's opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

For all sites:

[redacted]

For questions regarding SAEs, please contact:

[redacted]

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohn's disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Abbott Laboratories must be notified within 1 working day of a site's learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a study subject will be collected. Upon notification of a pregnancy Abbott will forward a form to the site, for the Investigator to complete and send back to Abbott. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to Abbott.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States, Canada and Puerto Rico. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott representative:

[redacted]

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by Abbott to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. In order to evaluate the impact of major protocol violations / deviations on the results of the study, additional analyses may be performed on the per-protocol population, which excludes all subjects with major protocol deviations. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation,

mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind study M06-806).

8.1.2.2 Primary Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subject's last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

The primary endpoint will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]
- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent, and post−treatment AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and

system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be 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 will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.4.1 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

8.1.5 Interim Analysis

There are no planned interim analyses.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix C.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by

local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to Abbott.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix D.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institution's IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subject's parent/legal guardian. The original signed ICF and Assent Form will be placed in the subject's medical record. An entry must also be made in the subject's dated source

documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subject's source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by Abbott. These forms will be used to transmit information collected during the study to Abbott and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case report forms must be legible and completed in indelible black ballpoint ink. Any

necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by Abbott personnel (or their representatives). Abbott (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by Abbott. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigator's meeting will be held with Abbott personnel, the Investigators and their study coordinators, the CRO's project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigator's meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality assurance check will be performed to ensure that the Investigator is complying with the

protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All data hand entered in the database will be verified by a double-key entry procedure at Abbott. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

Sites will provide Abbott (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of adalimumab. This information may be disclosed as deemed necessary by Abbott Laboratories to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by Abbott.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and Abbott. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and Abbott. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to Abbott or their designee.

Abbott may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Abbott terminates the study for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Abbott will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title: 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

Protocol Date: 26 August 2010

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohn's disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form

IRB	Institutional Review Board
ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N−telopeptide
OL	Open-Label
PCDAI	Pediatric Crohn's Disease Activity Index
PK	Pharmacokinetics
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohn's Disease

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Statistics
		Clinical
		Clinical
		Clinical

Appendix C. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigator's agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigator's agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigator's agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.

- If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union

Appendix D. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigator's qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix E. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

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Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix F. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Appendix G. Pediatric Crohn's Disease Activity Index (PCDAI)

							Score
1.	Abdominal pain rating						
	- None		= 0 p				
	- Mild - Brief, does not interfere with activities		= 5 p				
	- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p				
2.	Stools (per day)						
	- 0–1 liquid stools, no blood		= 0 p				
	- Up to 2 semi-formed with small blood, or 2–5 liquid		= 5 p				
	- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p				
3.	Patient Functioning, General Well-Being						
	- No limitation of activities, well		= 0 p				
	- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p				
	- Frequent limitation of activity, very poor		= 10 p				
LABORATORY							**Score**
4.	HCT: Male and female ≤ 10 years:			Male 11–14 years:			
		≥ 33	= 0 p		≥35	= 0 p	
		28-32	= 2.5 p		30-34	= 2.5 p	
		< 28	= 5 p		<30	= 5 p	
	Female 11–19 years:	≥ 34	= 0 p	Male 15–19 years:	≥37	= 0 p	
		29-33	= 2.5 p		32-36	= 2.5 p	
		< 29	= 5 p		<32	= 5 p	
5.	ESR (mm/hr)	< 20	= 0 p				
		20-50	= 2.5 p				
		> 50	= 5 p				
6.	Albumin (g/dL)	≥ 3.5	= 0 p				
		3.1-3.4	= 5 p				
		≤ 3.0	= 10 p				

EXAMINATION			**Score**
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥ 10%	= 10 p	
8. Height	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations (Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)			
	- None	= 0 p	
	- One	= 5 p	
	- ≥ Two	= 10 p	
TOTAL SCORE	**Pediatric Crohn's Disease Activity Index (PCDAI)**		

Appendix H. PCDAI User's Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohn's disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohn's disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 264: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48
- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216

The intent is to assess the normalcy vs. impairment of the subject's recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

$$\frac{\text{Present height} - \text{Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

    a. Velocity less than "Minus 2 SD" scores 10 points.

    b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

    c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	Minus 2SD	Minus 1SD	Mean
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix I. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0=none, 1=mild, 2=moderate, 3=severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0=generally well, 1=slightly underpar, 2=poor, 3=very poor, 4=terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil / Imodium / Loperamide /opiates for diarrhea 0=no, 1=yes	_____	X	30	
6. Abdominal mass 0=none, 2=questionable, 5=defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix J. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. **Add item requested for each day.**	**Crohn's Disease Activity Index Subject Diary Card**						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0=none, 1=mild, 2=moderate, 3=severe)							
Daily rating of general well being. (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)							

Subject Initials:_____ Subject's Signature:_____

Investigator or Designee's Signature:_____

Appendix K. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohn's disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I don't feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I don't think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I don't try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I don't feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix L. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix M. Day 70 Phone Call

Site Name / Number: _____

Subject Number:_____

Subject Initials:_____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to Abbott within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted].

Appendix N. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohn's disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix O. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctor's office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix P. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctor's office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctor's office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13- Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263*					

* Week 259 dose will only be taken if on every-week dosing schedule.

Appendix Q. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctor's office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

One pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

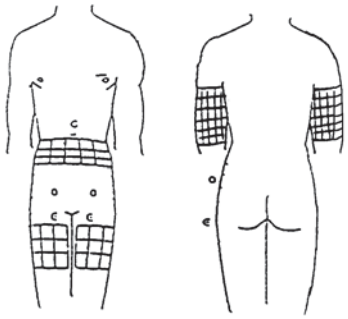
Remember to complete your dosing diary after each injection and to call the doctor's office if you are having problems administering your study drug.

General Information **PFS**

- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

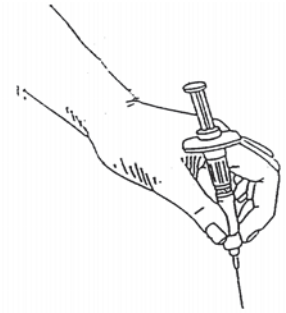
Injection Procedures **PFS**

1. Clean your workspace, gather your supplies, and wash your hands.



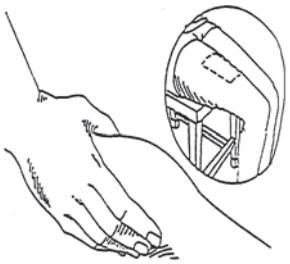
2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

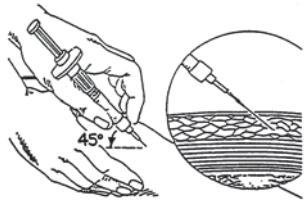


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

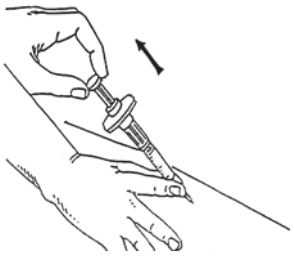
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

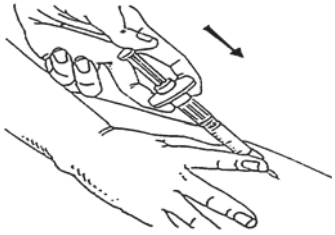


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



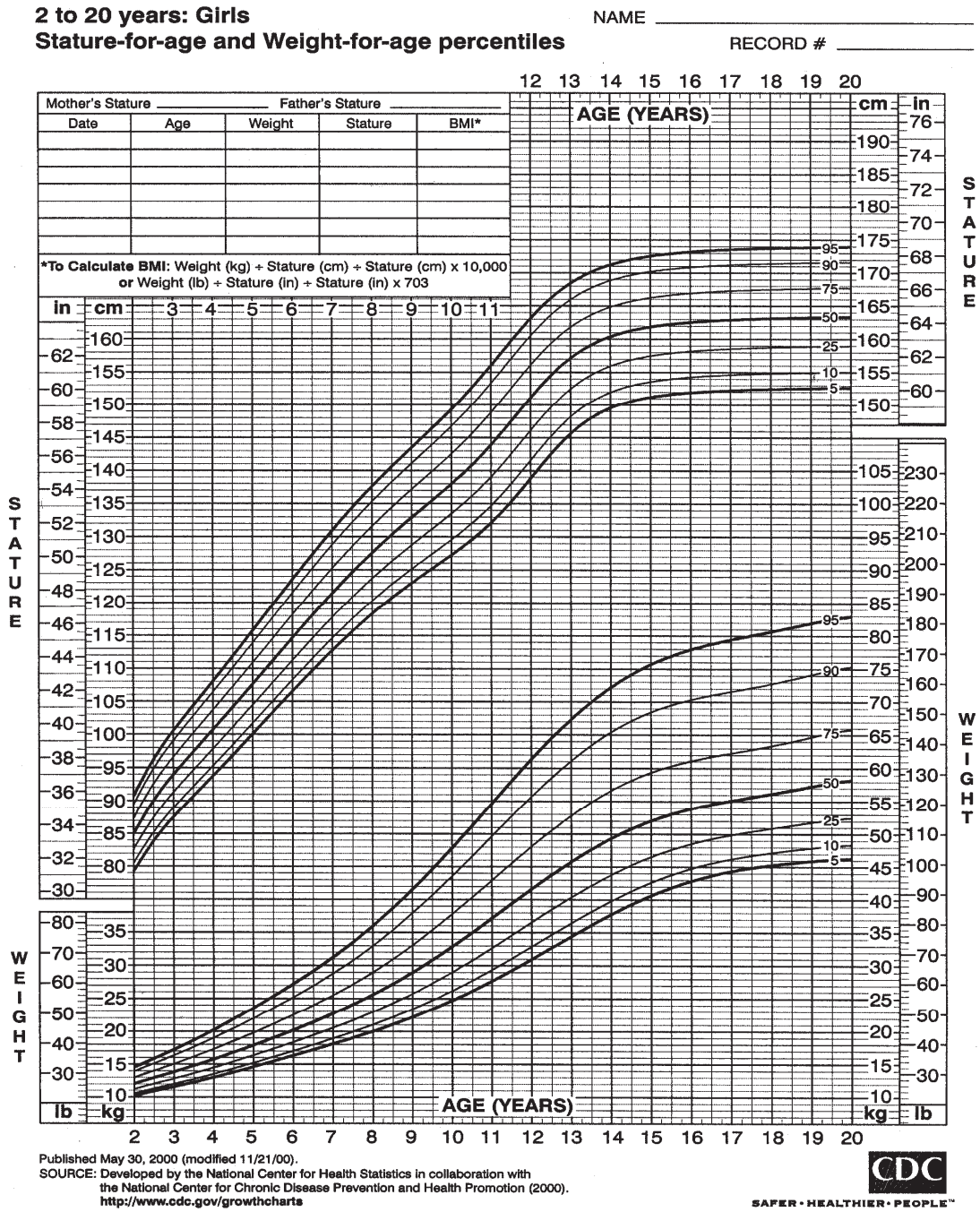
11. Remove needle while maintaining a 45-degree angle.

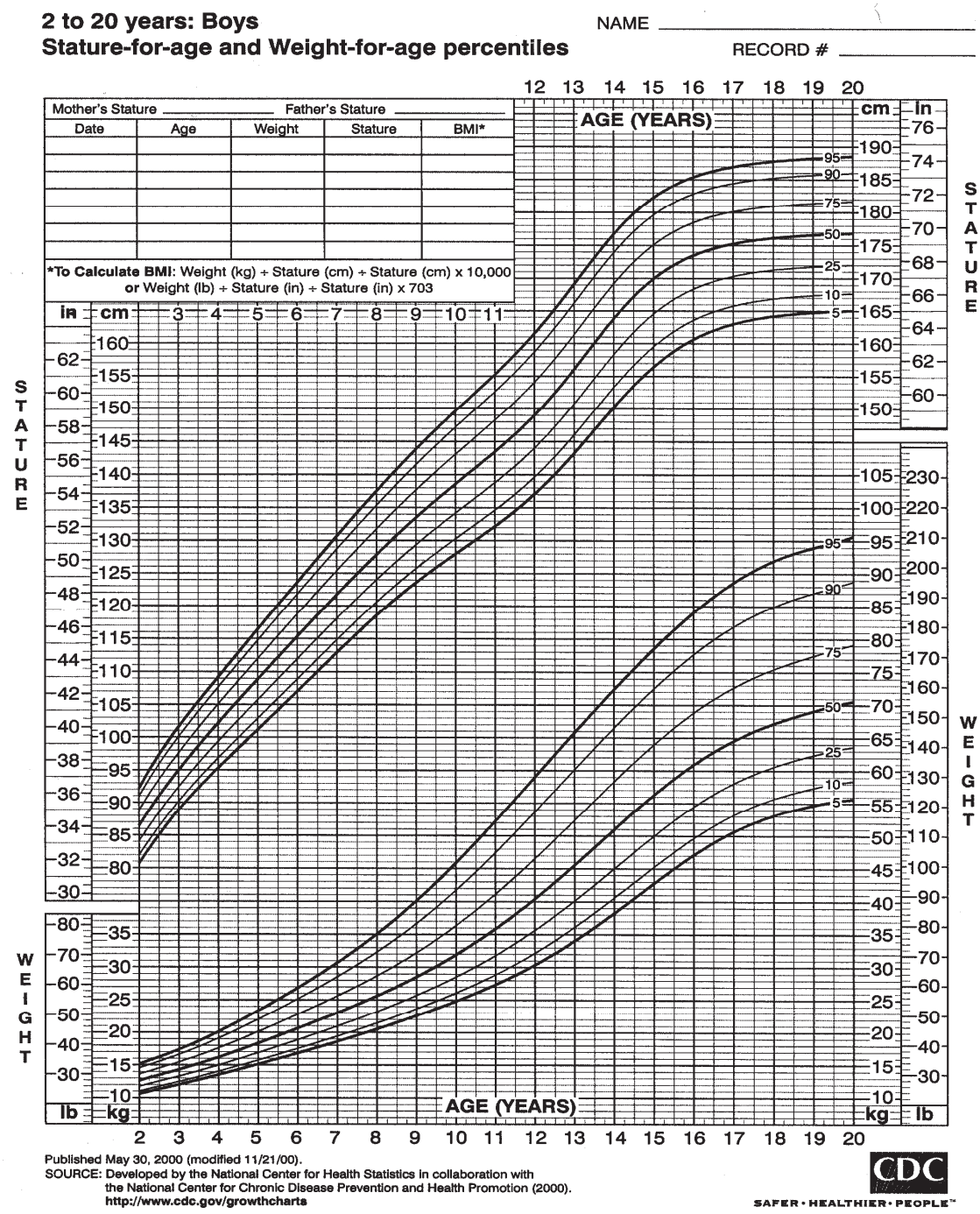
12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Appendix R. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER · HEALTHIER · PEOPLE™

Appendix S. Subject Abbott Laboratories Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix T. Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) - Caregiver

The following questions ask about the effect of your child's Crohn's disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

---

2. During the past seven days, how many hours did you miss from work because of problems associated with your child's Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your child's Crohn's disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your child's Crohn's disease affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your child's Crohn's disease *affected your work only a little, choose a low number. Choose a high number if your child's* Crohn's disease *affected your work a great deal.*

Consider only how much your child's Crohn's disease affected your productivity <u>while you were working</u>.

My child's Crohn's disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My child's Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your child's Crohn's Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your child's Crohn's Disease affected your activities only a little, choose a low number. Choose a high number if your child's Crohn's Disease affected your activities a great deal.

Consider only how much your child's Crohn's disease affected your ability to do your regular daily activities, other than work at a job.

My child's Crohn's disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My child's Crohn's disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:CD-Caregiver (US English)

Appendix U. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Emergency Contact:" previously read:

Has been changed to read:

Section 5.1 Overall Study Design and Plan: Description
First paragraph previously read:

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 55 sites that have enrolled subjects in the

M06−806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects are expected to enroll in this study.

Has been changed to read:

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 31 sites that have enrolled subjects in the M06-806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

Section 5.1 Overall Study Design and Plan: Description
Third paragraph previously read:

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. At the end of Study M06−806, a subject must be a responder to enroll in this trial. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

Has been changed to read:

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. A subject must be a responder at any time point during the M06-806 study. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

Section 5.1 Overall Study Design and Plan: Description
Eleventh paragraph previously read:

The duration of the study could last up to 104 weeks. Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

Has been changed to read:

The duration of the study could last up to 264 weeks (approximately 5 years). Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

This study will conclude approximately 12 weeks after the following criteria have been satisfied:

- Study drug receives country and local (if applicable) regulatory approval for pediatric Crohn's Disease.
- All applicable local reimbursement procedures are completed.

Sites will be notified once these criteria are met.

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

Table 1. Study Activities
Previously read:

Activity	Base-line	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104/ Early Term	Unscheduled visit	70-Day Follow-up Phone Call
Inclusion/exclusion criteria	X													
Informed consent	X													
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
CRP	X[a]				X		X		X			X		
ANA	X[a]			X								X		
Anti-dsDNA[f]	X[a]			X								X		
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X		

Table 1. Study Activities (Continued)

Activity	Base-line	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104/ Early Term	Unscheduled visit	70-Day Follow-up Phone Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X		
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI−CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X		
X-ray for bone age	X[a]						X					X		
Serum bone markers	X[a]				X		X		X			X		
Adverse events[i]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X		X[j]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, and 104/ET.
i. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
j. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

Has been changed to read:

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Inclusion/exclusion criteria	X											
Informed consent	X											
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X			X
ANA	X[a]			X								X
Anti-dsDNA[f]	X[a]			X								X
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X
X-ray for bone age	X[a]						X					X
Serum bone markers	X[a]				X		X		X			X
PK Blood Sample					X		X		X		X	
Anti-adalimumab blood levels (AAA)					X		X		X		X	
Adverse events[i]	X[a]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Inclusion/exclusion criteria															
Informed consent															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X		X		X		X		X		X		X	X	
Vital signs[c]	X		X		X		X		X		X		X	X	
Physical exam	X		X		X		X		X		X		X	X	
General LAB[d]	X		X		X		X		X		X		X	X	
Urinalysis[e]	X		X		X		X		X		X		X	X	
Erythrocyte sedimentation rate	X		X		X		X		X		X		X	X	
CRP			X		X		X		X				X		
ANA			X				X						X		
Anti-dsDNA[f]			X				X						X		
PCDAI	X		X		X		X		X		X		X	X	
CDAI[g]	X		X		X		X		X		X		X	X	
IMPACT III Questionnaire[h]	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264/ Early Term	Unsched Visit	70-Day Follow-up Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI − CD)	X		X		X		X		X		X		X	X	
X-ray for bone age			X				X						X	X	
Serum bone markers	X		X		X		X		X		X		X	X	
PK Blood Sample[i]	X		X		X		X		X		X		X	X	
Anti-adalimumab blood levels (AAA)[i]	X		X		X		X		X		X		X	X	
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X			X[k]	

Table 1. Study Activities (Continued)

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 144, 168, 192, 216, 240 and 264/ET.
i. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.
j. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
k. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

Section 5.3.1.1 Study Procedures
First paragraph previously read:

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs.

Has been changed to read:

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs. The site will call the subjects at Weeks 132, 156, 180, 204, 228 and 252 in order to collect any safety information from the subject as illustrated in Table 1.

Section 5.3.1.1 Study Procedures
Subsection Previous and Concomitant Medications
First paragraph, first sentence previously read:

Changes in concomitant medications will be assessed at each study visit from Baseline through Week 104/ET visit.

Has been changed to read:

Changes in concomitant medications will be assessed at each study visit from Baseline through the Week 264/ET visit.

Section 5.3.1.1 Study Procedures
Subsection Immunologic Laboratory Assessments
First paragraph previously read:

CRP assessments will be performed at Baseline (Week 52 of the M06-806 Study), Weeks 24, 48, 72 and 104/ET. Antinuclear antibody (ANA) will be performed at Baseline (Week 52 of the M06-806 Study), Week 12, and Week 104/ET. If an ANA

result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Has been changed to read:

CRP, adalimumab levels, anti-adalimumab antibody levels (AAA) and antinuclear antibody (ANA) assessments will be performed as indicated in Table 1. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Section 5.3.1.1 Study Procedures
Subsection Markers of Bone Metabolism
First sentence previously read:

Serum markers of bone metabolism will be measured at Baseline (Week 52 of the M06−806 Study), Weeks 24, 48, 72 and 104/ET.

Has been changed to read:

Serum markers of bone metabolism will be measured as indicated in Table 1.

Section 5.3.1.1 Study Procedures
Subsection IMPACT III Questionnaire
First paragraph, first sentence previously read:

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire at Baseline, Weeks 12, 24, 48, 72, and 104/ET as indicated in Table 1.

Has been changed to read:

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire as indicated in Table 1.

Section 5.3.1.1 Study Procedures
Subsection Bone Age
First sentence previously read:

An x-ray of the wrist for the assessment of bone age will be obtained at Baseline (Week 52 of M06-806), Week 48, and Week 104/ET to determine changes in bone maturation as indicated in Table 1.

Has been changed to read:

An x-ray of the wrist for the assessment of bone age will be obtained as indicated in Table 1.

Section 5.3.1.1 Study Procedures
Subsection Adverse Events
First paragraph, first sentence previously read:

Adverse events will be assessed at every study visit from Baseline through Week 104 / Early Termination visit.

Has been changed to read:

Adverse events will be assessed at every study visit from Baseline through the Week 264/ET visit.

Section 5.3.1.1 Study Procedures
Subsection Study Drug Administration
First paragraph, first sentence previously read:

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical personnel to reinforce proper aseptic SC injection technique.

Has been changed to read:

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical professional to reinforce proper aseptic SC injection technique.

Section 5.3.2 Drug Concentration Measurements
Previously read:

No drug concentration measurements will be obtained in this trial.

Has been changed to read:

Blood samples for the assay of adalimumab and AAA serum concentrations will be collected at Baseline and every 24 weeks thereafter. In addition, blood samples for adalimumab and AAA concentration analysis will also be collected if a subject meets flare criteria and dose escalated to ew dosing. Study visits in which blood samples will be collected are listed in Table 1. At each visit, blood samples will be collect prior to study drug administration at each visit.

The time that each blood sample is collected will be recorded to the nearest minute in the source documents and on the appropriate CRF.

Section 5.3.2.1 Collection of Samples for Analysis
Add: new section

<u>Collection of Samples for Adalimumab Analysis</u>

Blood samples for adalimumab analysis will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 samples are planned to be collected per subject for the analysis of adalimumab concentrations.

Collection of Samples for AAA Analysis

Blood samples for AAA assay will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at visits indicated in Table 1. All samples will be obtained immediately prior to dosing at visits indicated in Table 1. Sufficient blood will be collected to provide approximately 2 mL serum. Blood will be allowed to clot for 30 minutes at room temperature before centrifugation.

A maximum of 13 blood samples are planned to be collected per subject for AAA analysis.

Section 5.3.2.2 Handling/Processing of Samples
Add: new section

The blood samples for adalimumab and AAA, assay will be centrifuged within 30 to 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with the type of sample (serum, SRM), the protocol number, subject number, the study week and the assay (PK-Adalimumab, AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder until shipped. Sites that do not have access to a −20°C or colder freezer will need to ship the samples the day they are collected. (Detailed instructions provided in the ICON Laboratory Manual).

Section 5.3.2.3 Disposition of Samples
Add: new section

The PK and AAA samples will be shipped to ICON with all other samples being shipped to ICON. Refer to the ICON Lab Manual for further instruction. Neither Abbott nor ICON will supply dry ice for this study. Study sites will identify a dry ice source and purchase the necessary dry ice.

Section 5.3.2.4 Measurement Methods
Add: new section

Serum concentrations of adalimumab will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories. Only serum samples that have adalimumab levels < 2.0 μg/mL will be selected for AAA concentration measurement.

Serum concentrations of AAA will be determined using a validated ELISA method under the supervision of the Drug Analysis Department at Abbott Laboratories.

Section 5.3.3 Efficacy Variables
Second paragraph previously read:

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, and healthcare resource utilization (unscheduled outpatient visits).

Has been changed to read:

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, healthcare resource utilization (unscheduled outpatient visits), adalimumab levels and anti-adalimumab levels (AAA).

Section 5.3.4 Safety Variables
Add: second paragraph

Treatment-emergent events will be summarized and reported by treatment group and by AAA status (AAA+ versus AAA-).

Section 5.3.5 Pharmacokinetic Variables
Add: new section

Serum concentrations of adalimumab and AAA will be determined from samples collected at the study visits listed in Table 1.

Section 5.4.1 Discontinuation of Individual Subjects
Second paragraph, first sentence previously read:

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 104/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

Has been changed to read:

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 264/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

Section 5.4.3 Stopping Rules
Previously read:

An independent Data Monitoring Committee (DMC) will meet to discuss unblinded data from the study every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations. In addition, an ad-hoc DMC meeting will be convened if either of the following criteria is met.

- The overall proportion of subjects with SAEs, with an investigator-assessed causality of at least possibly related or higher, evaluated on a per subject basis, exceeds 0.20 (or 20%); or
- The overall proportion of subjects with serious infectious SAEs, evaluated on a per subject basis, exceeds 0.20 (or 20%).

If either of the above criteria is met, the DMC will meet within 2 weeks to consider whether or not to recommend a temporary suspension of enrollment.

Has been changed to read:

An independent Data Monitoring Committee (DMC) will meet to discuss data from the study approximately every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations.

Section 6.5 Adverse Event Reporting
Previously read:

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

For all sites:

For questions regarding SAEs, please contact:

Has been changed to read:

In the event of an SAE, whether related to study drug or not, the investigator will notify one of the following people by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE.

For all sites:

For questions regarding SAEs, please contact:

Section 6.6 Pregnancy
Third paragraph previously read:

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Has been changed to read:

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States, Canada and Puerto Rico. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Section 7.0 Protocol Deviations
First paragraph and contact previously read:

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott representative:

[redacted]

Has been changed to read:

The investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the following Abbott representative:

Section 8.1.4.1 Pharmacokinetic Analyses
Add: new section

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non missing observations (nnmiss), mean, median, standard deviation, coefficient of variation, minimum, and maximum. The relationship between adalimumab concentrations and efficacy and/or safety variables may be explored. Additional analysis may be performed.

Appendix A. List of Abbreviations and Definition of Terms
Add:

AAA	Anti-adalimumab antibody
PK	Pharmacokinetics

Appendix B. List of Protocol Signatories
Add: new appendix

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical
		Clinical

Appendix G. PCDAI User's Guide and Guideline for Reference Weight and Reference Height
"Item 7," second line previously read:

From Baseline to Week 104: use weight from previous visit

Has been changed to read:

From Baseline to Week 264: use weight from previous visit

Appendix G. PCDAI User's Guide and Guideline for Reference Weight and Reference Height
"Item 8," bullets previously read:

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72, use height from Week 48

Has been changed to read:

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72 to Week 96, use height from Week 48

- From Week 96 to Week 120, use height from Week 72
- From Week 120 to Week 144, use height from Week 96
- From Week 144 to Week 168, use height from Week 120
- From Week 168 to Week 192, use height from Week 144
- From Week 192 to Week 216, use height from Week 168
- From Week 216 to Week 240, use height from Week 192
- From Week 240 to Week 264, use height from Week 216

Appendix H. Crohn's Disease Activity Index (CDAI)
Footnote previously read:

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Has been changed to read:

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up. To ensure consistency across all sites and to take into account the varying growth rates of subjects in this study, the IBW should be calculated at each visit.

Appendix O. Subject Dosing Diary
"Week 97 - Week 104" previously read:

Week 97 - Week 104

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103*					

*The dose at Week 103 will only be taken if you are on weekly dosing.

Has been changed to read:

Week 97 - Week 108

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103					
	Week 104					
	Week 105					
	Week 106					
	Week 107					
	Week 108					

Appendix O. Subject Dosing Diary
Add:

Week 109 - Week 120

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 109					
	Week 110					
	Week 111					
	Week 112					
	Week 113					
	Week 114					
	Week 115					
	Week 116					
	Week 117					
	Week 118					
	Week 119					
	Week 120					

Week 121 - Week 144

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 121					
	Week 122					
	Week 123					
	Week 124					
	Week 125					
	Week 126					
	Week 127					
	Week 128					
	Week 129					
	Week 130					
	Week 131					
	Week 132					
	Week 133					
	Week 134					
	Week 135					
	Week 136					
	Week 137					
	Week 138					
	Week 139					
	Week 140					
	Week 141					
	Week 142					
	Week 143					
	Week 144					

Week 145 - Week 168

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 145					
	Week 146					
	Week 147					
	Week 148					
	Week 149					
	Week 150					
	Week 151					
	Week 152					
	Week 153					
	Week 154					
	Week 155					
	Week 156					
	Week 157					
	Week 158					
	Week 159					
	Week 160					
	Week 161					
	Week 162					
	Week 163					
	Week 164					
	Week 165					
	Week 166					
	Week 167					
	Week 168					

Week 169 - Week 192

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 169					
	Week 170					
	Week 171					
	Week 172					
	Week 173					
	Week 174					
	Week 175					
	Week 176					
	Week 177					
	Week 178					
	Week 179					
	Week 180					
	Week 181					
	Week 182					
	Week 183					
	Week 184					
	Week 185					
	Week 186					
	Week 187					
	Week 188					
	Week 189					
	Week 190					
	Week 191					
	Week 192					

Week 193 - Week 216

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 193					
	Week 194					
	Week 195					
	Week 196					
	Week 197					
	Week 198					
	Week 199					
	Week 200					
	Week 201					
	Week 202					
	Week 203					
	Week 204					
	Week 205					
	Week 206					
	Week 207					
	Week 208					
	Week 209					
	Week 210					
	Week 211					
	Week 212					
	Week 213					
	Week 214					
	Week 215					
	Week 216					

Week 217 - Week 240

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 217					
	Week 218					
	Week 219					
	Week 220					
	Week 221					
	Week 222					
	Week 223					
	Week 224					
	Week 225					
	Week 226					
	Week 227					
	Week 228					
	Week 229					
	Week 230					
	Week 231					
	Week 232					
	Week 233					
	Week 234					
	Week 235					
	Week 236					
	Week 237					
	Week 238					
	Week 239					
	Week 240					

Week 241 - Week 263

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 241					
	Week 242					
	Week 243					
	Week 244					
	Week 245					
	Week 246					
	Week 247					
	Week 248					
	Week 249					
	Week 250					
	Week 251					
	Week 252					
	Week 253					
	Week 254					
	Week 255					
	Week 256					
	Week 257					
	Week 258					
	Week 259					
	Week 260					
	Week 261					
	Week 262					
	Week 263*					

* Week 259 dose will only be taken if on every-week dosing schedule.

Appendix P. Self Injection Instructions
Heading Study Drug Dosing Schedule
Third paragraph, first sentence previously read:

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96) will be done during your visit, at the doctor's office.

Has been changed to read:

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216 and 240) will be done during your visit, at the doctor's office.

Appendix R. Abbott Laboratories Site Drug Accountability Form
Appendix title previously read:

Abbott Laboratories Site Drug Accountability Form

Has been changed to read:

Subject Abbott Laboratories Site Drug Accountability Form

Document Approval

Study M06807 - 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 - Amendment 2 - EudraCT 2007-006494-90 - 26Aug2010

Version: 1.0 **Date:** 30-Aug-2010 03:16:40 PM **Abbott ID:** 08302010-00AB619FD3E1E0-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	26-Aug-2010 06:28:02 PM	Approver
	26-Aug-2010 10:16:22 PM	Author
	30-Aug-2010 11:52:43 AM	Approver
	30-Aug-2010 03:16:39 PM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Incorporating Administrative Changes 1 and 2 and Amendment 1

Abbott Number / Investigational Product:	Adalimumab	
Date:	10 October 2008	
Development Phase:	3	
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe.	
EudraCT Number:	2007-006494-90	
Investigator:	Multicenter (Investigator information on file at Abbott Laboratories).	
Sponsor:	European Union Countries:	Non European Union Countries:
	Abbott GmbH & Co.KG Knollstrasse 50 67061 Ludwigshafen, Germany	Abbott Laboratories, US 100 Abbott Park Road Abbott Park, IL 60064
Emergency Contact:	[redacted]	

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Section 5.2.1 (Inclusion Criteria): Inclusion Criterion Number 2 updated to clarify that a subject must be a responder during the M06-806 study. Because hematocrit scores are needed to determine if a subject is eligible to enter the study, there is not enough time to have the labs drawn at Week 52 of M06-806/Baseline M06-807 and have the results back from the lab prior to the subject rolling over. In addition, Abbott does not want to exclude subjects who have responded at another time point within the M06-806 study.
- Amend the stopping rules in Section 5.4.3 as follows:

  The rate of possibly related SAEs or higher, on a per subject per year basis in excess of 0.45, was changed to the proportion of SAEs, possibly related or higher, on a per subject basis in excess of 0.20.

  Rationale: *The new stopping boundary of 0.20 is based on the 'Any SAEs' proportion of 0.20 reported in the Infliximab Pediatric Crohn's Disease trial. The original rate of 0.45/patient-years was chosen based on SAE data from adult trials in Rheumatoid Arthritis (RA). This rate could allow for as many as 5 events based on the 11.1 patient-years accrued as at the time of the first DMC meeting on 20 Mar 2008, although only 1 SAE of at least possibly drug related had actually been reported. (**Reference:** "Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children," Hyams et al., Gastroenterology Vol. 132, No. 3, pages 863-873, March 2007). During a teleconference between Abbott and the DMC on 03 Jun 2008, the DMC reviewed and agreed with the revised* stopping rules.
- The overall rate, in excess of 0.09 infectious SAEs on a per patient per year basis was changed to the overall proportion of infectious SAEs in excess of 0.20 on a per subject basis.

  Rationale: *The new stopping boundary of 0.20 is calculated as 2.5 × (the 'Serious Infection' proportion of 0.08 reported in the Infliximab Pediatric Crohn's Disease trial). The choice of 2.5 × the Serious Infection rate from the*

infliximab study data was arbitrary, but based on clinical judgment. The serious infection rate reported in the infliximab trial ranged from 5.7% to 22.2%, and the rate for the combined infliximab group was 8.0%. Based on clinical judgment, the team decided to choose a value in multiples of 8% but not exceeding the high extreme of 22.2%. Thus the value of 20% (which resulted from 2.5× 8.0%) was thought to be clinically reasonable for a stopping boundary. The original rate of 0.09/patient-years was chosen based on 'Serious Infectious SAE' data from adult Rheumatoid Arthritis (RA) trials. This rate is not applicable because it is not suitable for a stopping boundary. At the time of the first DMC meeting (20 Mar 2008), when the study was experiencing slow enrollment and had only accrued 11.1 patient-years of follow-up, this old rate only allowed just 1 infectious SAE (that is, 1/11.1 = 0.09/patient-years). This meant that even with 2 infectious SAEs, the study would cross the original stopping boundary. This is obviously not an acceptable option in this pediatric Crohn's study where infections are part of the underlining nature of the disease. During a teleconference between Abbott and the DMC on 03 Jun 2008, the DMC reviewed and agreed with the revised stopping rules.

- The paragraph in the protocol with the text "If either of these criteria is met, no new enrollment will occur until the DMC or the SSC makes their recommendations" was changed to "If either of the above criteria is met, the DMC will meet within 2 weeks to consider whether or not to recommend a temporary suspension of enrollment."

  Rationale: *The original text calling for the study to be "temporarily suspended if either of the above criteria is met" was copied from a previous adult Crohn's protocol. The DMC review of the SAEs and safety data indicated that there was no need to suspend the study at all, since infections are part of the underlining nature of Crohn's disease in children. The revised wording will allow the DMC to first consider a meeting to review the safety data in detail and render its recommendation on whether or not to temporarily suspend the trial. During a teleconference between Abbott and the DMC on 03 Jun 2008, the DMC reviewed and agreed with the revised text in the protocol.*

- Section 12.2 regarding publication has been removed.

  Rationale: *Publication of data from this study is covered in the site contract and is not required in the protocol.*

- Administrative Changes:
  - Section 1.0 (Title Page) and 14.0 (Investigator's Agreement): Updated date of protocol.
  - Section 3.0 (Introduction): Approvals from other indications have been updated to reflect the most current data available.
  - Section 5.5.1 (Treatment Administered): A typographical error has been corrected to clarify dose of 20 mg/0.4 ml and not 20 mg/0.8 ml.
  - Section 5.5.4 (Selection and Timing of Dose for Each Subject: A typographical error has been corrected to remove "of the" in sentence, "All clinic visits for the subject should be scheduled on the same day of the as the Baseline visit for this study."
  - Section 6.5 (Adverse Event Reporting): Safety Hotline address and contact information have been updated.
  - Section 15.0 (Reference) updated to add reference for the current guidelines for the treatment of latent TB.
  - Appendix C (Documents Required Prior to Initiation of the Study): Updated to reflect the current regulatory requirements.
  - Appendix D (Responsibilities of the Clinical Investigator): Updated to reflect the current regulatory requirements.
  - Appendix E [CDC Treatment of Tuberculosis Infection (Preventive Therapy)]: Updated with the current guidelines for the treatment of latent TB
  - Appendix H (PCDAI User's Guide and Guideline for Reference Weight and Reference Height): Updated to clarify from Week 48 to Week 72 and from post Week 72, use height from Week 48. Original text states Week 52, however there is no Week 52 visit, which is why it has been changed to Week 48.

- Appendix L (Excluded Medications): Updated to state any previous anti-TNF medication except infliximab before the M06-806 study.
- Appendix M (Day 70 Phone Call): Faxing contact information has been updated.

- Minor typographical formatting errors corrected throughout protocol.

See Appendix T for an itemized list made to this protocol under Amendment 1.

2.0 Table of Contents

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3.0 Introduction

Crohn's Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is

heterogeneous with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohn's disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population. In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohn's disease. In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active

treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved

clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew), adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and

133 subjects continued in a 32-week double blind segment. Clinically significant improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients. There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigator's Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease. The subject

population will consist of subjects who participated in and successfully completed the M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigator's discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigator's discretion. For a detailed description of the study please see Section 5.0.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 55 sites that have enrolled subjects in the M06−806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects are expected to enroll in this study.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. At the end of Study M06−806, a subject must be a responder to enroll in this trial. A responder is

defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare is 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 subject's previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects' body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohn's treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

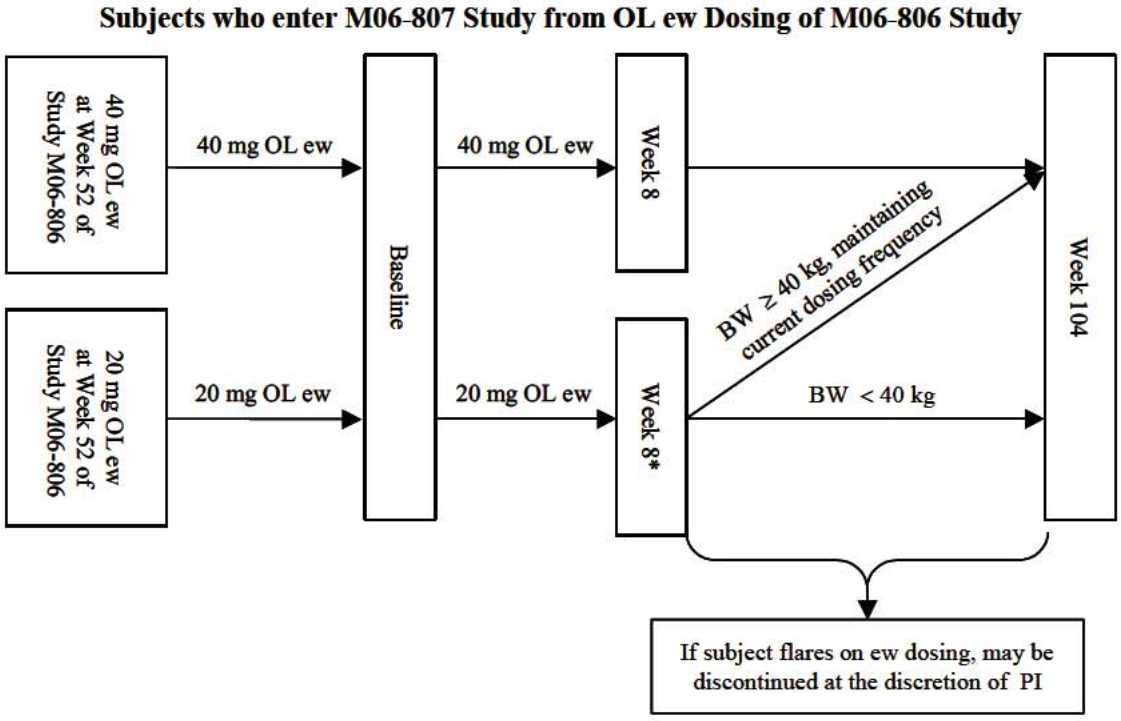
Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohn's specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 104 weeks. Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

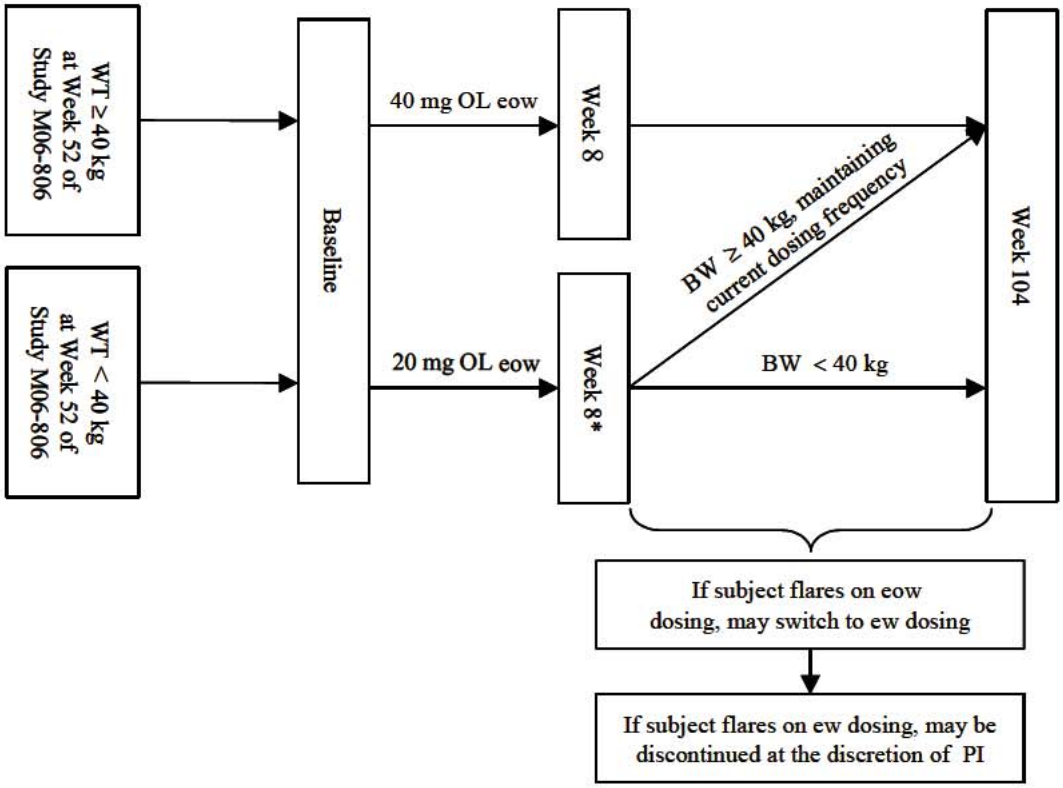
A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at any time point during the M06-806 study.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subject's parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subject's diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohn's disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma−in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the

opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the Abbott Laboratories Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the Abbott Laboratories Medical Monitor identified in Section 7.0

5.2.3.2 Concomitant Therapy

Adjustments of Crohn's related concomitant treatments, including Crohn's related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohn's related antibiotics or Crohn's related concomitant treatments are allowed according to the Investigator's medical judgment. These adjustments may be performed without prior discussion with the Abbott Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohn's related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and Subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg	5 mg/week
	≤ 10 mg	2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix K).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Base-line	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104/ Early Term	Unscheduled visit	70-Day Follow-up Phone Call
Inclusion/exclusion criteria	X													
Informed consent	X													
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
CRP	X[a]				X		X		X			X		
ANA	X[a]			X								X		
Anti-dsDNA[f]	X[a]			X								X		
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X		

Table 1. Study Activities (Continued)

Activity	Base-line	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104/ Early Term	Unscheduled visit	70-Day Follow-up Phone Call
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X		
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI−CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X		
X-ray for bone age	X[a]						X					X		
Serum bone markers	X[a]				X		X		X			X		
Adverse events[i]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X		X[j]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, and 104/ET.
i. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
j. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institution's IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subject's source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through Week 104/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subject's casebook from the previous study (M06-806). They will not be required to be captured in the subject's casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subject's M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix N) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be

obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP assessments will be performed at Baseline (Week 52 of the M06-806 Study), Weeks 24, 48, 72 and 104/ET. Antinuclear antibody (ANA) will be performed at Baseline (Week 52 of the M06-806 Study), Week 12, and Week 104/ET. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the site's local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured at Baseline (Week 52 of the M06−806 Study), Weeks 24, 48, 72 and 104/ET. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohn's Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix F. Instructions for completing the PCDAI score is located in Appendix G.

Crohn's Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix G.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix H.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire at Baseline, Weeks 12, 24, 48, 72, and 104/ET as indicated in Table 1. A copy of the questionnaire is located in Appendix J.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix M, Appendix S).

The subject's parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained at Baseline (Week 52 of M06-806), Week 48, and Week 104/ET to determine changes in bone maturation as indicated in Table 1. Sites should use the Greulich and Pyle method for

reading the x−ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by Abbott Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr) / SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through Week 104 / Early Termination visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s)

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix L for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical personnel to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subject's home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at

each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study drug administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix O.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/- 3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/- 3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06−806).

5.3.2 Drug Concentration Measurements

No drug concentration measurements will be obtained in this trial.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, and healthcare resource utilization (unscheduled outpatient visits).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subject's legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non−melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.

- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 104/ET Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

Abbott reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss unblinded data from the study every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the

study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations. In addition, an ad-hoc DMC meeting will be convened if either of the following criteria is met.

- The overall proportion of subjects with SAEs, with an investigator-assessed causality of at least possibly related or higher, evaluated on a per subject basis, exceeds 0.20 (or 20%); or
- The overall proportion of subjects with serious infectious SAEs, evaluated on a per subject basis, exceeds 0.20 (or 20%).

If either of the above criteria is met, the DMC will meet within 2 weeks to consider whether or not to recommend a temporary suspension of enrollment.

5.5 Treatments

5.5.1 Treatments Administered

All study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.4 mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the study Baseline visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

5.5.2.1 Packaging and Labeling

The following information will appear on the pre-filled syringe or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number

- Route of Administration
- Excipients
- Blank spaces to write the subject's identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix P.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes are to be stored protected from light at 2° to 8°C/ 36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until Abbott GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to Abbott Laboratories.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call−in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06−806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the

dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix O).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix R. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes will be inventoried by the site and verified by the CRA. The used syringes will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit boxes, subject diaries and by visually counting the syringes in the sharp's container whenever possible. Used sharp's containers should never be opened. Each subject will be given their own sharps disposal container to store expelled syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohn's disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 was developed using an analogous approach as that studied in the adult CD population. Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD. A model based on the JRA population was chosen because the body weight range will closely parallel that in a juvenile CD population. Escalation to weekly dosing will provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Abbott as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

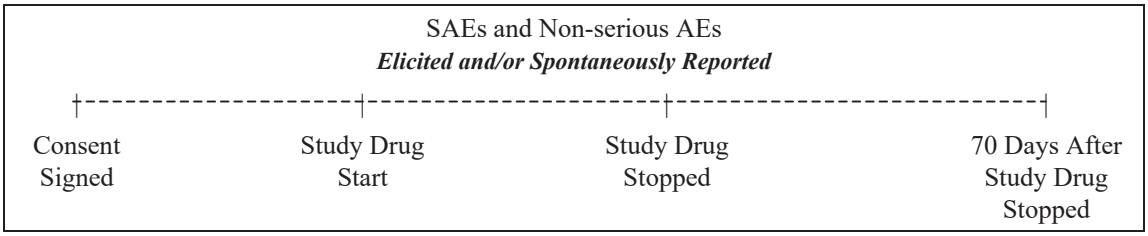
If an Investigator's opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the Investigator will notify Abbott by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

For sites located within North America:

SAE Support Hotline

[redacted]

For sites located outside North America:

For questions regarding SAEs, please contact:

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohn's disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Abbott Laboratories must be notified within 1 working day of a site's learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a study subject will be collected. Upon notification of a pregnancy Abbott will forward a form to the site, for the Investigator to complete and send back to Abbott. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to Abbott.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the following Abbott representative:

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by Abbott to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. In order to evaluate the impact of major protocol violations / deviations on the results of

the study, additional analyses may be performed on the per-protocol population, which excludes all subjects with major protocol deviations. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind study M06-806).

8.1.2.2 Primary Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subject's last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

The primary endpoint will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]

- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent, and post−treatment AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be 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 will be flagged in reference to the normal range (low,

normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.5 Interim Analysis

There are no planned interim analyses.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix B.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to Abbott.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix C.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate) of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institution's IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subject's parent/legal guardian. The original signed ICF and Assent Form will be placed in the

subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subject's source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by Abbott. These forms will be used to transmit information collected during the study to Abbott and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case

report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by Abbott personnel (or their representatives). Abbott (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by Abbott. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigator's meeting will be held with Abbott personnel, the Investigators and their study coordinators, the CRO's project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigator's meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality

assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All data hand entered in the database will be verified by a double-key entry procedure at Abbott. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

Sites will provide Abbott (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of adalimumab. This information may be disclosed as deemed necessary by Abbott Laboratories to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by Abbott.

12.2 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and Abbott. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and Abbott. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to Abbott or their designee.

Abbott may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Abbott terminates the study for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Abbott will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title: 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

Protocol Date: 10 October 2008

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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2. Loftus Jr. EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504-17.

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5. Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin; a statewide population-based study. J Pediatr 2003;143(4):525-31.

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohn's disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form
IRB	Institutional Review Board

ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N−telopeptide
OL	Open-Label
PCDAI	Pediatric Crohn's Disease Activity Index
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohn's Disease

Appendix B. Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigator's agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigator's agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the investigator's agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.

- If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is required to be completed for each investigator and/or subinvestigator who is a resident of the European Union

Appendix C. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigator's qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix D. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

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Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix E. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Appendix F. Pediatric Crohn's Disease Activity Index (PCDAI)

							Score
1.	Abdominal pain rating						
	- None		= 0 p				
	- Mild - Brief, does not interfere with activities		= 5 p				
	- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p				
2.	Stools (per day)						
	- 0–1 liquid stools, no blood		= 0 p				
	- Up to 2 semi-formed with small blood, or 2–5 liquid		= 5 p				
	- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p				
3.	Patient Functioning, General Well-Being						
	- No limitation of activities, well		= 0 p				
	- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p				
	- Frequent limitation of activity, very poor		= 10 p				
LABORATORY							**Score**
4.	HCT: Male and female ≤ 10 years:			Male 11–14 years:			
		≥ 33	= 0 p		≥35	= 0 p	
		28-32	= 2.5 p		30-34	= 2.5 p	
		< 28	= 5 p		<30	= 5 p	
	Female 11–19 years:	≥ 34	= 0 p	Male 15–19 years:	≥37	= 0 p	
		29-33	= 2.5 p		32-36	= 2.5 p	
		< 29	= 5 p		<32	= 5 p	
5.	ESR (mm/hr)	< 20	= 0 p				
		20-50	= 2.5 p				
		> 50	= 5 p				
6.	Albumin (g/dL)	≥ 3.5	= 0 p				
		3.1-3.4	= 5 p				
		≤ 3.0	= 10 p				

EXAMINATION			Score
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥ 10%	= 10 p	
8. Height	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations (Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)			
	- None	= 0 p	
	- One	= 5 p	
	- ≥ Two	= 10 p	
TOTAL SCORE	**Pediatric Crohn's Disease Activity Index (PCDAI)**		

Appendix G. PCDAI User's Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohn's disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohn's disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 104: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72, use height from Week 48

The intent is to assess the normalcy vs. impairment of the subject's recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

   $$\frac{\text{Present height} - \text{Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

   a. Velocity less than "Minus 2 SD" scores 10 points.

   b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

   c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	**Minus 2SD**	**Minus 1SD**	**Mean**
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix H. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0=none, 1=mild, 2=moderate, 3=severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0=generally well, 1=slightly underpar, 2=poor, 3=very poor, 4=terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil / Imodium / Loperamide /opiates for diarrhea 0=no, 1=yes	_____	X	30	
6. Abdominal mass 0=none, 2=questionable, 5=defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix I. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. **Add item requested for each day.**	**Crohn's Disease Activity Index Subject Diary Card**						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0=none, 1=mild, 2=moderate, 3=severe)							
Daily rating of general well being. (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)							

Subject Initials:_____ Subject's Signature:_____

Investigator or Designee's Signature:_____

Appendix J. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohn's disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I don't feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I don't think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I don't try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I don't feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix K. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix L. Day 70 Phone Call

Site Name / Number: _____

Subject Number:_____

Subject Initials:_____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to Abbott within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted]

Appendix M. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohn's disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix N. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctor's office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix O. Subject Dosing Diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctor's office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctor's office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13- Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 104

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103*					

*The dose at Week 103 will only be taken if you are on weekly dosing.

Appendix P. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96) will be done during your visit, at the doctor's office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

One pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

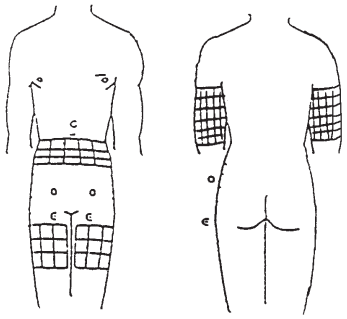
Remember to complete your dosing diary after each injection and to call the doctor's office if you are having problems administering your study drug.

General Information **PFS**

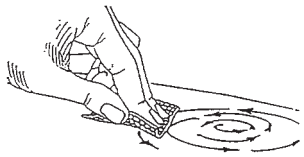
- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

Injection Procedures **PFS**

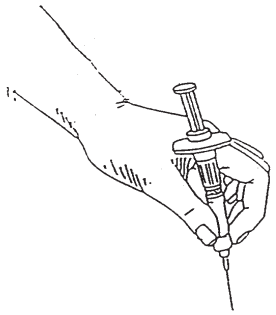
1. Clean your workspace, gather your supplies, and wash your hands.



2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

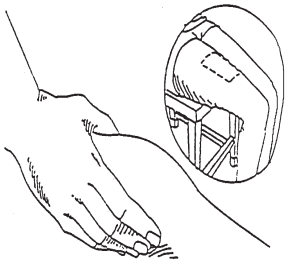


3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

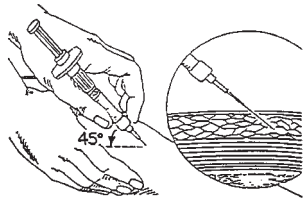


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

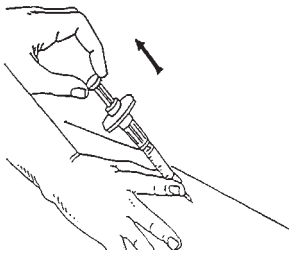
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

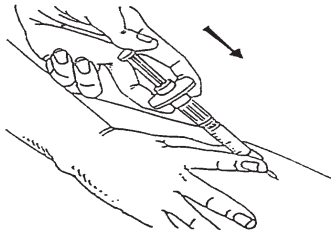


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



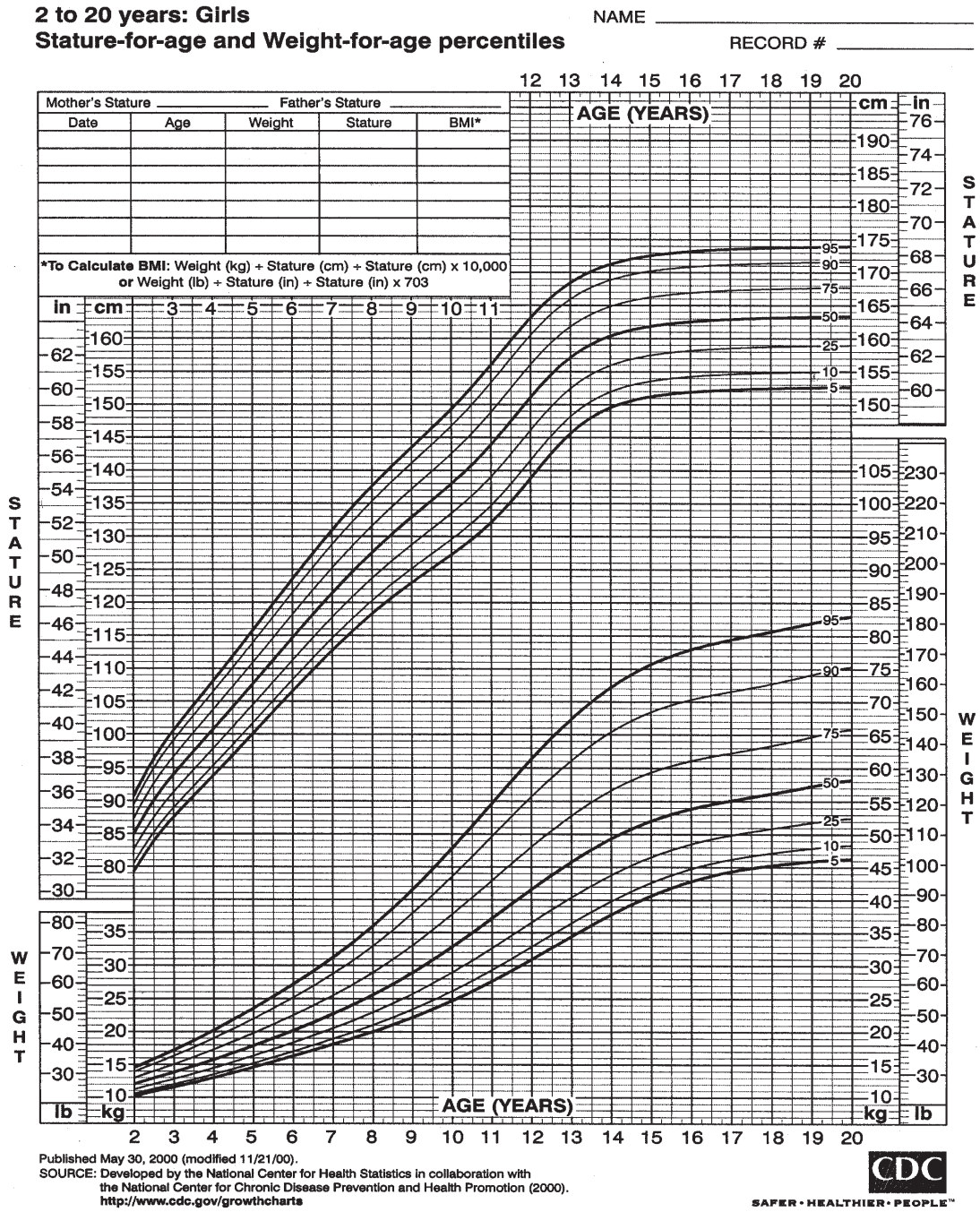
11. Remove needle while maintaining a 45-degree angle.

12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

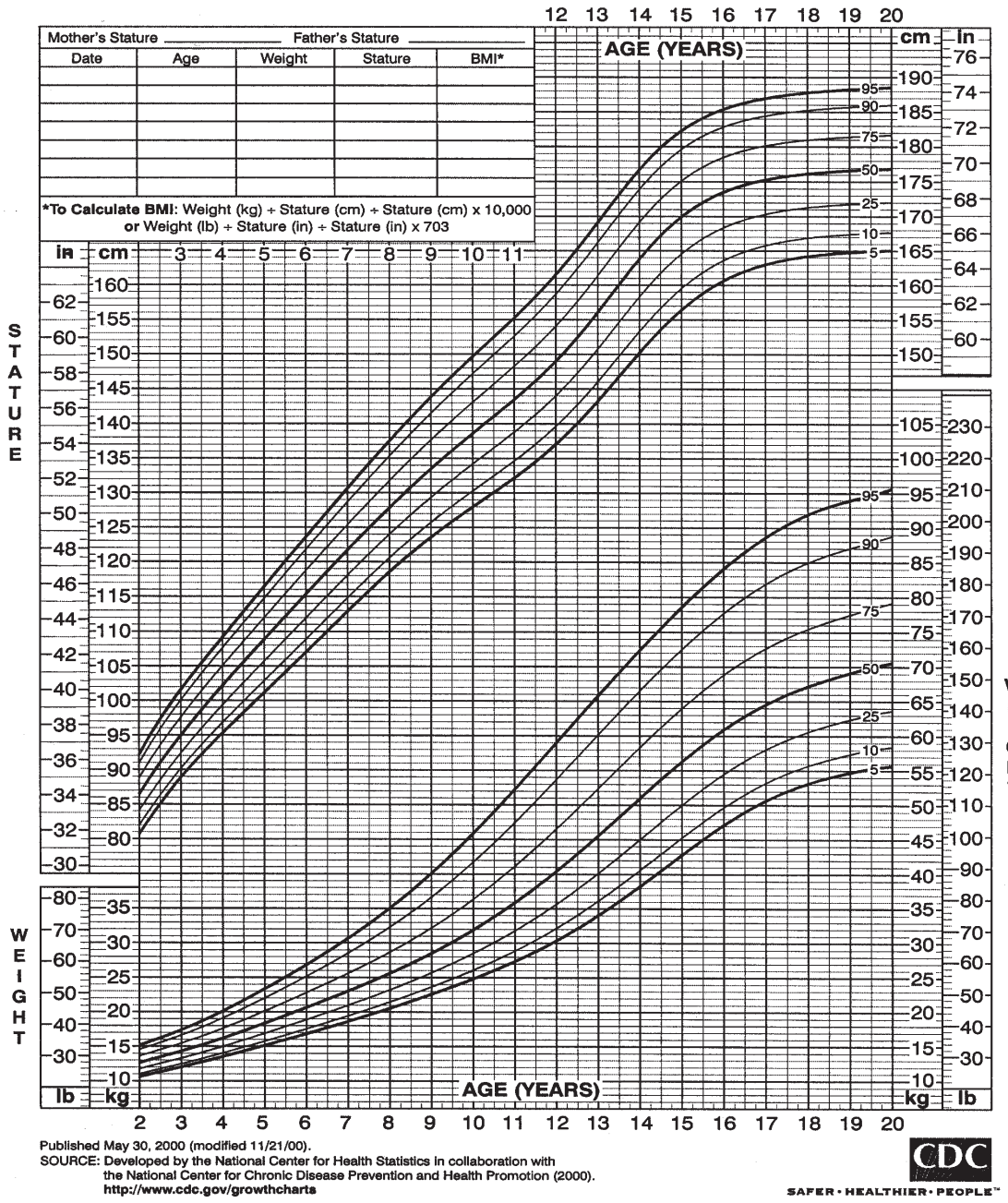
Appendix Q. Standard Weights



2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC
SAFER · HEALTHIER · PEOPLE™

Appendix R. Abbott Laboratories Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix S. Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) - Caregiver

The following questions ask about the effect of your child's Crohn's disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

---

2. During the past seven days, how many hours did you miss from work because of problems associated with your child's Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your child's Crohn's disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your child's Crohn's disease affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your child's Crohn's disease *affected your work only a little, choose a low number. Choose a high number if your child's* Crohn's disease *affected your work a great deal.*

Consider only how much your child's Crohn's disease affected your productivity while you were working.

My child's Crohn's disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My child's Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your child's Crohn's Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your child's Crohn's Disease affected your activities only a little, choose a low number. Choose a high number if your child's Crohn's Disease affected your activities a great deal.

Consider only how much your child's Crohn's disease affected your ability to do your regular daily activities, other than work at a job.

My child's Crohn's disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My child's Crohn's disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:CD-Caregiver (US English)

Appendix T. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 3.0 Introduction
Tenth paragraph, first sentence previously read:

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through July 2007 in a total of 69 countries.

Has been changed to read:

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through August 2008 in a total of 76 countries.

Section 3.0 Introduction
Add: fifth and sixth sentences to tenth paragraph

In December 2007 and January 2008, respectively, adalimumab was approved for the treatment of psoriasis in adult patients in the EU, Canada and USA. Additionally, adalimumab was approved for the treatment of juvenile idiopathic arthritis in the USA in February 2008.

Section 3.0 Introduction
Eleventh paragraph, second sentence previously read:

In the CD development program, adalimumab was studied in over 1400 subjects in three pivotal studies (two induction studies and a maintenance study).

Has been changed to read:

In the CD development program, adalimumab was studied in over 1400 adult subjects in three pivotal studies (two induction studies and a maintenance study).

Section 5.2.1 Inclusion Criteria
Criterion number 2 previously read:

Subject must be a responder at Week 52 of Study M06-806.

Has been changed to read:

Subject must be a responder at any time point during the M06-806 study.

Section 5.4.3 Stopping Rules
Following first paragraph, first and second bullets previously read:

- The overall rate of SAEs, with an Investigator assessed causality of at least possibly related or higher, evaluated on a per subject year basis, exceeds 0.45 (0.15 SAEs/subject every four months), or
- The overall rate of serious infectious SAEs evaluated on a per subject year basis, exceeds 0.09 (.03 SAEs/subject every four months).

Has been changed to read:

- The overall proportion of subjects with SAEs, with an investigator-assessed causality of at least possibly related or higher, evaluated on a per subject basis, exceeds 0.20 (or 20%); or
- The overall proportion of subjects with serious infectious SAEs, evaluated on a per subject basis, exceeds 0.20 (or 20%).

Section 5.4.3 Stopping Rules
Second paragraph previously read:

If either of these criteria is met, no new enrollment will occur until the DMC or the SSC makes their recommendation.

Has been changed to read:

If either of the above criteria is met, the DMC will meet within 2 weeks to consider whether or not to recommend a temporary suspension of enrollment.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Fourth paragraph, second sentence previously read:

All clinic visits for the subject should be scheduled on the same day of the Baseline visit for this study.

Has been changed to read:

All clinic visits for the subject should be scheduled on the same day as the Baseline visit for this study.

Section 6.5 Adverse Event Reporting
Second paragraph and address previously read:

For sites located within North America:

SAE Support Hotline

Has been changed to read:

For sites located within North America:

SAE Support Hotline

Section 12.2 Publication
Delete: entire section

All information concerning adalimumab and Abbott Laboratories' operations, such as patent application, formulas, manufacturing processes, basic scientific data or formulation information supplied by Abbott Laboratories which have not been previously published are considered confidential by Abbott Laboratories and shall remain the sole property of Abbott Laboratories. The Investigator agrees to use this information only to perform this study and will not use it for other purposes including publications and presentations without Abbott Laboratories' written consent.

It is understood by the Investigator that the information developed in the clinical trial will be used by Abbott Laboratories in connection with the development of adalimumab and, therefore, may be disclosed as required to other clinical Investigators, other pharmaceutical companies, to the U.S. FDA and to other regulatory agencies. It is understood that there is an obligation to provide Abbott Laboratories with complete test results and all data resulting from this study and to provide direct access to source data/documents for study related monitoring, audits, IEC/IRB review, and regulatory inspection.

Section 15.0 Reference List
Add: new reference number 32

32. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2006 April.

Appendix B. Documents Required Prior to Initiation of the Study
Previously read:

As sponsor of a clinical trial, Abbott has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the Investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical trial, the Investigator will be asked to provide the following documentation.

1. A signed and dated Investigator's agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the Investigator's agreement to comply with the appropriate regulations governing the conduct of the study.

3. A current *curriculum vita* of the Investigator. If subinvestigators will participate in the study, *curriculum vita* for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

    - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
    - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.

- If the Investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure forms must be completed by each Investigator and all Subinvestigators identified on the Form FDA 1572. A Financial Disclosure, EU consent, is required to be completed for each Investigator and/or Subinvestigator who is a resident of the European Union.

Has been changed to read:

As sponsor of a clinical study, Abbott has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with Good Clinical Practices and applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed and dated Investigator's agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the investigator's agreement to comply with the appropriate regulations governing the conduct of the study.

   A signed and dated Investigator Information and Agreement Form certifying the

investigator's agreement to comply with the appropriate (e.g., ICH GCP) regulations governing the conduct of the study. These will be required only for sites that are recruited under this amendment, or when existing sites update study documentation.

3. Current curriculum vitae for the investigator. If subinvestigators will participate in the study, curriculum vitae for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.
   - If the investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure Certification forms must be completed by each investigator and all subinvestigators identified on the Form FDA 1572 or Investigator Information and Agreement Form. A Financial Disclosure, EU Consent, is

required to be completed for each investigator and/or subinvestigator who is a resident of the European Union

Appendix C. Responsibilities of the Clinical Investigator
Previously read:

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigator's qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Has been changed to read:

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigator's qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix D. CDC Treatment of Tuberculosis Infection (Preventive Therapy)
Previously read:

When taken as prescribed, isoniazid therapy is highly effective in preventing latent tuberculosis (TB) infection from progressing to TB disease.

Who should receive preventive therapy?

The following persons should be given high priority for preventive therapy if they have positive skin test results, regardless of their age:

1. Persons with 5 mm induration on their PPD who will receive a TNF inhibitor,

2. Persons known to have or suspected of having HIV infection (5 mm or greater of induration),
3. Persons who have been in close contact with someone who has infectious TB disease (5 mm or greater),
4. Persons whose skin test results converted from negative to positive within the past 2 years (10 mm or greater),
5. Persons with abnormal chest radiographs who have never been treated for TB or who have been inadequately treated for TB (5 mm or greater),
6. Persons who have injected drugs and who are HIV seronegative (10 mm or greater), and
7. Persons with organ transplants and other immunosuppressed subjects (5mm or greater),
8. Persons who have medical conditions that increase the risk for TB (10 mm or greater). These conditions include diabetes mellitus, gastrectomy, some hematologic and reticuloendothelial diseases, and end-stage renal disease, silicosis, and body weight that is 10% or more below ideal.

In addition, in the absence of any of the above risk factors, persons in the following groups should be evaluated for preventive therapy if their reaction to the tuberculin skin test is 10 mm or greater:

1. Foreign-born persons from countries where TB is common;
2. Medically underserved, low-income populations; and
3. Residents of long-term care facilities.

In addition, staff of facilities in which a person with infectious TB disease would pose a risk to large numbers of susceptible persons (e.g., health care facilities, correctional facilities, and nursing homes) should be evaluated for preventive therapy if they have a positive skin test result.

Persons who have a positive reaction to the tuberculin skin test should not be given preventive therapy until the possibility of TB disease has been ruled out. In addition, persons who are being considered for preventive therapy should be evaluated for medical contraindications, such as:

1. Previous isoniazid-associated hepatic injury,
2. History of severe adverse reactions to isoniazid, and;
3. Acute or active liver disease.

Also, special precautions should be taken for some persons who are receiving preventive therapy.

Precautions are indicated for:

1. Persons who are older than 35,
2. Persons who abuse alcohol,
3. Pregnant women,
4. Persons with chronic liver disease,
5. Persons with peripheral neuropathy, and
6. Persons who in the past have stopped using isoniazid because of adverse effects.

Regimens for Preventive Therapy

The usual preventive therapy regimen is 9 months of daily isoniazid, in a dosage of 5 milligrams per kilogram of body weight. The maximum daily dose is 300 milligrams. HIV-infected persons should receive 9 months of preventive therapy. An alternative regimen for adults is 4 months of rifampin.

For persons with a strain of *M. tuberculosis* that is resistant to isoniazid but susceptible to rifampin, CDC recommends the use of rifampin alone for 4 months for preventive therapy.

Adverse Reactions

The major toxic effect of isoniazid is hepatitis. The risk for hepatitis increases with alcohol consumption. Isoniazid may also cause peripheral neuropathy. Persons at risk for neuropathy—for example, persons who abuse alcohol and persons with diabetes—should be given pyridoxine, or vitamin B-6, in conjunction with isoniazid therapy.

Subjects should be educated about the signs and symptoms of toxicity to isoniazid, and they should be monitored monthly by appropriately trained personnel. No more than a 1 month supply of medicine should be dispensed at any visit. If signs or symptoms of toxicity appear, isoniazid should be stopped immediately, and the subject reevaluated. Subjects should not be given isoniazid preventive therapy if they cannot be monitored monthly.

Has been changed to read:

Centers for Disease Control and Prevention
Tuberculosis Information
Treatment of Tuberculosis Infection (Preventive Therapy), Latent Tuberculosis Infection (LBTI)[32]

TB Elimination

Treatment of Latent Tuberculosis Infection (LTBI)

Introduction

Treatment of latent TB infection (LTBI) is essential to controlling and eliminating TB in the United States. Treatment of LTBI substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI.

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is ≥5mm:

- HIV-infected persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is ≥10 mm:

- Recent arrivals (<5 years) from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is ≥15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care for persons with TB infection or disease.

Regimens

For persons suspected of having LTBI, treatment of LTBI should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e., HIV infection, suspected drug resistance, pregnancy, or treatment of children). Listed in the table are the regimens; please refer to *Targeted Tuberculin Testing and Treatment of Latent TB Infection*[1] for detailed information for the treatment of LTBI.

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.[2] (Clinicians should continue the appropriate use of RIF and PZA in multidrug regimens for the treatment of active TB disease.[3])

April 2006 Website - www.cdc.gov/tb Page 1 of 2

Table: Drug Regimens for Treatment of LTBI

Drugs	Duration (months)	Interval	Minimum doses
Isoniazid	9	Daily	270
		Twice weekly	76
Isoniazid	6	Daily	180
		Twice weekly	52
Rifampin	4	Daily	120
Rifampin/Pyrazinamide	Generally should not be offered for treatment of LTBI[2]		

Monitoring

Isoniazid or Rifampin Alone
Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

Rifampin/Pyrazinamide or Rifabutin/ Pyrazinamide
A TB/LTBI expert should be consulted prior to the use of this regimen.

CDC is collecting reports of all severe adverse events (e.g., liver injury, metabolic acidosis, anaphylaxis, seizure, severe dermatitis) leading to hospitalization or death of a person receiving treatment of latent tuberculosis infection that occurred after January 1, 2004. Report these adverse events to the Division of Tuberculosis Elimination at 404-639-8401 or LManangan@cdc.gov.

Additional Information

1. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. MMWR 2000;49(No.RR- 6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

2. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. MMWR 2003; 52 (No.31). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

3. ATS/CDC. Treatment of Tuberculosis. MMWR 2003;49 (No. RR-11). www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Appendix G. PCDAI User's Guide and Guideline for Reference Weight and Reference Height
Subsection Physical Examination, "Item 8. Height"
Second, third and fourth bullets previously read:

- From Week 24 to Week 52, use height from Baseline visit
- From Week 52 to Week 72, use height from Week 24
- From post Week 72, use height from Week 52

Has been changed to read:

- From Week 24 to Week 48, use height from Baseline visit
- From Week 48 to Week 72, use height from Week 24
- From Week 72, use height from Week 48

Appendix K. Excluded Medication
Last medication on the list of Appendix K previously read:

Any previous anti-TNF medication except infliximab before the study (including adalimumab).

Has been changed to read:

Any previous anti-TNF medication except infliximab before the M06-806 study (including adalimumab).

Appendix L. Day 70 Phone Call
Fax information at the end of Appendix L previously read:

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Paragon at [redacted].

Has been changed to read:

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Abbott at [redacted]

Appendix O. Subject Dosing Diary
Table "Study Entry – Week 4"
Previously read:

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 2					
	Week 3					
	Week 4					

Has been changed to read:

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 1					
	Week 2					
	Week 3					
	Week 4					

Document Approval

Study M06807-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, AMD 1, EudraCT 2007-006494-90 - 10Oct2008

Version: 1.0 **Date:** 15-Oct-2008 03:28:30 PM **Abbott ID:** 10152008-00AB619D1AD665-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	10-Oct-2008 06:23:28 PM	Approver
	10-Oct-2008 09:19:08 PM	Approver
	13-Oct-2008 09:27:53 PM	Approver
	15-Oct-2008 03:28:22 PM	Approver

1.0 Title Page

CLINICAL TRIAL PROTOCOL M06-807

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

Abbott Number / Investigational Product:	Adalimumab	
Date:	11 January 2008	
Development Phase:	3	
Study Design:	A multi-center, open-label safety and tolerability pediatric study in the United States, Canada and Europe	
EudraCT Number:	2007-006494-90	
Investigator:	Multicenter (Investigator information on file at Abbott Laboratories).	
Sponsor:	European Union Countries:	Non European Union Countries:
	Abbott GmbH & Co.KG Knollstrasse 50 67061 Ludwigshafen, Germany	Abbott Laboratories, US 100 Abbott Park Road Abbott Park, IL 60064
Emergency Contact:	[redacted]	

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

2.0 Table of Contents

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3.0 Introduction

Crohn's Disease (CD) is a chronic, debilitating, and currently incurable inflammatory disease that can affect the entire digestive system as well as extraintestinal organs. CD is primarily manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract[1] which can consist of mucosal edema, aphthous and linear ulcerations, asymmetrical narrowing and strictures. Noncaseating granulomas are virtually diagnostic in the correct clinical setting. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of cases often in combination with colitis, occurring in 50% of cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown.

The incidence in North America is similar to that in other western nations and is estimated from 3.1 to 14.6 cases per 100,000 person years and prevalence ranges from 26 to 199 cases per 100,000 persons.[2] The disease can affect persons of any age but the most common age of onset is in the second and third decades with a female preponderance. While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood.[3]

In addition, the incidence of CD in patients less than 18 years of age appears to be increasing in both North America and Europe.[4,5] Reported incidence rates range from 1.2 to 4.9 per 100,000 persons in the UK, Europe, and North America[6-12] with one study reporting an incidence of 4.6 per 100,000 persons in the United States.[5] CD has been reported at all ages but is rare in early childhood. In one study of patients with CD, 17 years of age and younger, 9.1% of the patients were diagnosed before the age of 6.[13] In a second study of patients diagnosed with CD before the age of 15, 7.5% of the patients were under the age of 5.[14]

Despite obvious physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients and is

heterogeneous with regard to anatomic localization and clinical severity.[5,15,16] The unique aspect of this disease in children is its impact on nutrition and growth, with marked growth retardation being a prominent component of the disease in this age group.[17-19] The use of accepted methodologies for assessing nutritional status, including the anthropometric measures of height, weight, triceps skin fold thickness and mid arm circumference as well as linear growth (height velocity and assessment of height velocity for chronological age "z-score") have documented the growth impairment that can occur in this age group, and also have been used to assess the efficacy of interventions.[20] Profound impairment of bone formation and increased bone resorption are associated complications and are related to the effect of glucocorticoids,[21,22] delayed puberty,[22,23] decreased mobility,[24] as well as to the effects of cytokines on bone formation.[25]

Initial symptoms are often subtle, and there is an average delay of almost six months between onset of symptoms and diagnosis. The most common presentation is with abdominal pain, diarrhea, loss of appetite and weight loss. However, isolated weight loss, anorexia, perianal disease and extraintestinal manifestations can occur in the absence of GI symptoms in a substantial number of patients.

The general approach to the treatment of CD in children is similar to adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improved quality of life, and avoidance of disease and drug related complications. Restoration and/or preservation of normal growth and pubertal development are additional therapeutic goals. The medical armamentarium is likewise similar to adults and includes induction of remission with corticosteroids, and ongoing maintenance therapy of immunomodulators, aminosalicylates and nutritional therapy. Anti-tumor necrosis factor (TNF) therapy with infliximab has been evaluated for the therapy of CD in this age group as it has in adults. The FDA and EMEA have recently approved Infliximab for use in children with CD.

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Adalimumab consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. It binds specifically with high affinity to the soluble and transmembrane forms of TNFα and inhibits the binding of TNFα with its receptors.

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) on 31 Dec 2002 in the United States (US), on 08 Sep 2003 in the European Union (EU) and through July 2007 in a total of 69 countries. Indication extensions to include treatment of psoriatic arthritis and early RA were granted in the EU on 01 Aug 2005 and in the US on 03 Oct 2005. A further indication extension to include treatment of ankylosing spondylitis was approved in the EU on 01 Jun 2006 and was approved in the US on 28 Jul 2006. Adalimumab was approved for the treatment of Crohn's disease in the United States on 27 Feb 2007, in the European Union on 04 Jun 2007 and in Canada on 05 July 2007 for the adult population.

Adalimumab has been shown to be a safe and effective treatment of moderately to severely active Crohn's disease. In the CD development program, adalimumab was studied in over 1400 subjects in three pivotal studies (two induction studies and a maintenance study).

Study M02-403 was a multicenter, randomized, double-blind, placebo-controlled Phase 2/3 study to evaluate the efficacy and safety of adalimumab for the induction of remission in subjects with moderate to severe CD.[26] A total of 299 subjects were randomized to receive one of four proposed induction treatment regimens (three active treatment groups or placebo): adalimumab 160 mg at Baseline (Week 0) followed by 80 mg at Week 2, adalimumab 80 mg at Baseline followed by 40 mg at Week 2, adalimumab 40 mg at Baseline followed by 20 mg at Week 2 or placebo at Baseline and

Week 2. Eligible subjects could not have been previously treated with any anti TNF agent. Only the group of subjects treated with adalimumab 160/80 mg had a statistically significantly greater remission rate at Week 4 (primary endpoint) compared to placebo (35.5% vs. 12.2%; p = 0.001). In addition, statistically significantly greater proportions of subjects in the adalimumab 160/80 mg group than in the placebo group experienced clinical response CR-100 (48.7% and 24.3%, respectively) and clinical response CR-70 (57.9% and 36.8%, respectively) at Week 4.

Study M04-691, a second induction study, was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of adalimumab as induction treatment for subjects with moderate to severe CD who either initially responded to administration of infliximab but stopped responding or were intolerant.[27] A total of 325 subjects were randomized to receive adalimumab 160/80 mg or placebo. Eligible subjects must have previously been treated with infliximab and discontinued use due to loss of response to or intolerance to infliximab therapy. The proportion of subjects who achieved clinical remission at Week 4 (primary endpoint) was statistically significantly greater in the adalimumab 160/80 mg group compared to the placebo group (21.4% vs. 7.2%). The proportion of subjects achieving clinical response CR-100 and CR-70 at Week 4 was statistically significantly greater in the adalimumab 160/80 mg group (38.4% and 51.6%, respectively) compared to the placebo group (24.7% and 33.7%, respectively).

Study M02-404 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of adalimumab for the maintenance of clinical remission in subjects with moderate to severe CD.[27] A total of 854 subjects (both naïve to or previously treated with TNF antagonists [primarily infliximab]) were enrolled and received open-label adalimumab 80 mg at Baseline (Week 0) and adalimumab 40 mg at Week 2. At Week 4, subjects were stratified by responder status (subjects who achieved clinical response CR-70) and previous anti-TNF use and were randomized in a 1:1:1 ratio to one of three blinded treatment groups: adalimumab 40 mg every week (ew),

adalimumab 40 mg every other week (eow), or placebo. Subjects who met clinical response CR-70 after Week 8 could be tapered from corticosteroids.

The proportion of Week 4 responders (N = 499) who achieved clinical remission at Weeks 26 and 56 (co-primary endpoint) were statistically significantly greater 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). The differences between the adalimumab 40 mg eow and adalimumab 40 mg ew groups at both of these time points were not statistically significant. The median time in first clinical remission was greater in the adalimumab 40 mg eow group (378 days) compared to the placebo group (127 days). 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. Approximately six times as many subjects treated with adalimumab maintenance therapy compared to placebo were able to discontinue corticosteroids for at least 90 days and achieve remission at Week 26 and Week 56. Efficacy was independent of Baseline C-reactive protein (CRP), concomitant therapies, such as corticosteroids or immunosuppressants, or prior anti-TNF experience. The adalimumab safety profile in CD was similar to that seen in the other rheumatologic populations previously studied, except for expected manifestations of CD.

Currently, there are two ongoing extension studies of adalimumab therapy in adult subjects with CD. M04-690 trial is a long-term safety and tolerability study of repeated administration of adalimumab in adult subjects with CD who had previously participated in M02-404 or M04-691. The other trial is a long-term open-label extension study following the initial first-year study period of the M02-433 study.

The efficacy and safety of adalimumab in children has recently been demonstrated in juvenile rheumatoid arthritis (JRA).[28] One hundred and seventy-one pediatric patients (4 to 17 years of age) were initially enrolled into a 16-week open label segment and 133 subjects continued in a 32-week double blind segment. Clinically significant improvements were noted in ACR30, ACR50 and ACR70 as well as other indices of arthritis activity. Adverse events (AEs) were similar as those noted in adult RA patients.

There were no deaths, malignancies, or opportunistic infections, including tuberculosis (TB). Thirteen serious adverse events (SAEs) in 8 subjects were observed in the 16-week open label portion of the study. These included 4 subjects with JRA, one patient with two episodes of leukopenia/neutropenia, and one case each of femur fracture, herpes simplex, and pneumonia. Six SAEs were observed in 6 subjects (2 placebo, 4 adalimumab) during the 32-week double blind portion (closed head injury, gastroduodenitis, retinal detachment, appendicitis, abdominal pain and urinary tract infection). Infections, AEs at least possibly related to study drug, and injection site reactions were reported by similar proportions of patients in all treatment groups during the double-blind therapy (32 weeks).

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. TB has also been observed in subjects treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[29]

TNF antagonists, including adalimumab, have been associated with cases of malignancy and demyelinating disease. Serious allergic adverse reactions have been reported in RA subjects following subcutaneous (SC) administration of adalimumab; none were reported in the CD program.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology, and safety experience can be found in the current Investigator's Brochure.

The goal of this study is to demonstrate the efficacy of adalimumab in the maintenance of clinical response and to demonstrate the long-term safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease. The subject population will consist of subjects who participated in and successfully completed the M06-806 study and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807. Qualifying subjects will administer open-label adalimumab by SC

injection. Subjects receiving every other weekly therapy who continue to have a disease flare or develop another flare may be switched to every week therapy at the investigator's discretion. Subjects receiving weekly therapy who continue to have a disease flare or develop another flare may be withdrawn from the study at the Investigator's discretion. For a detailed description of the study please see Section 5.0.

4.0 Study Objective

The objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with Crohn's disease who participated in, and successfully completed, Protocol M06-806 through Week 52 and who meet all the inclusion and none of the exclusion criteria of Protocol M06-807.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This study is a multi-center, open-label study of the human anti-TNF monoclonal antibody adalimumab. Approximately 55 sites that have enrolled subjects in the M06−806 clinical trial will participate in the M06-807 clinical trial. Approximately 130 pediatric subjects are expected to enroll in this study.

The Week 52 visit from the M06-806 study will be the Baseline Visit for those subjects entering study M06-807. The visit window for M06-806 Week 52 visit is 364 ± 7 days from the Baseline Visit date of M06-806.

Subjects may be allowed to enroll in the M06-807 study if they have participated in, and successfully completed Protocol M06-806 through Week 52. At the end of Study M06−806, a subject must be a responder to enroll in this trial. A responder is defined as a subject who had a PCDAI score that was at least 15 points lower than the M06-806 baseline score.

All subjects will be on open-label maintenance therapy. Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg at Baseline will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg at Baseline will receive 20 mg eow of adalimumab. Beginning at Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare is 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 subject's previous visit.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg to ≥ 40 kg from the Baseline (Week 52 of the M06-806 Study) visit. The site will enter the subjects' body weight into the Interactive Voice Response System (IVRS) and the dose will be adjusted, if applicable.

Reductions in concomitant therapy will be allowed for Crohn's treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

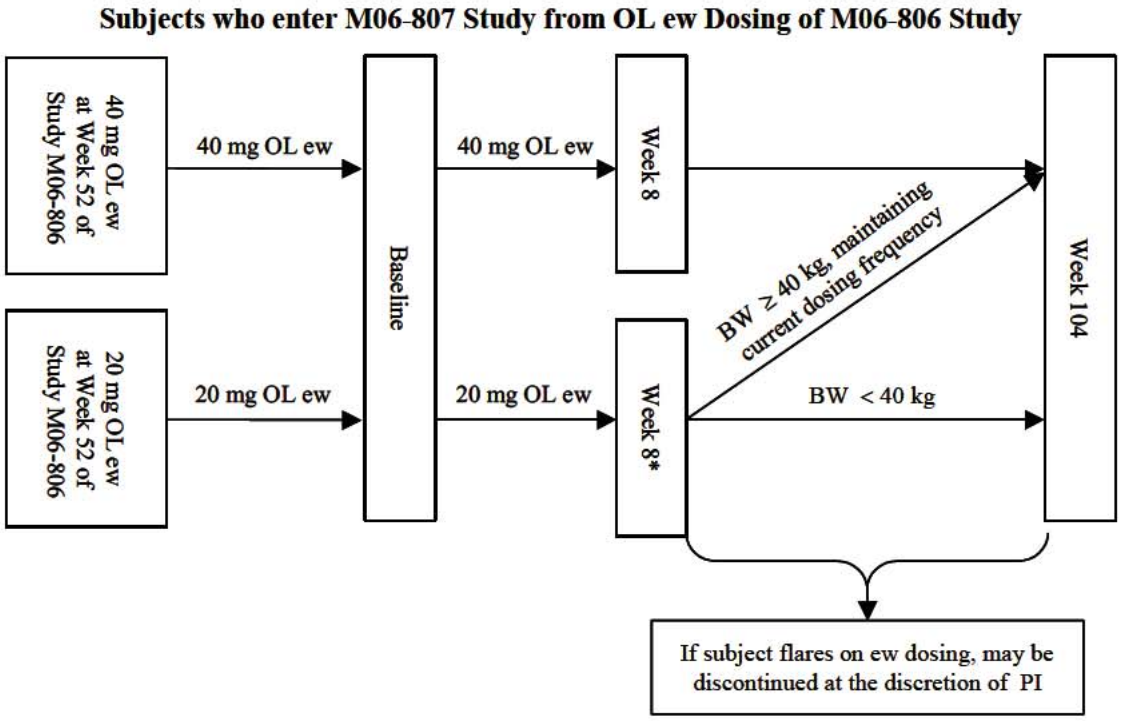
Subjects may be allowed to decrease prednisone (or equivalent) and budesonide if qualifications are met (please see Section 5.2.3.2 for required timing and rate of taper).

Subjects may be allowed to adjust their Crohn's specific concomitant medications as specified in Section 5.2.3.2.

The duration of the study could last up to 104 weeks. Subjects who complete, or who early terminate from the study will be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new AEs.

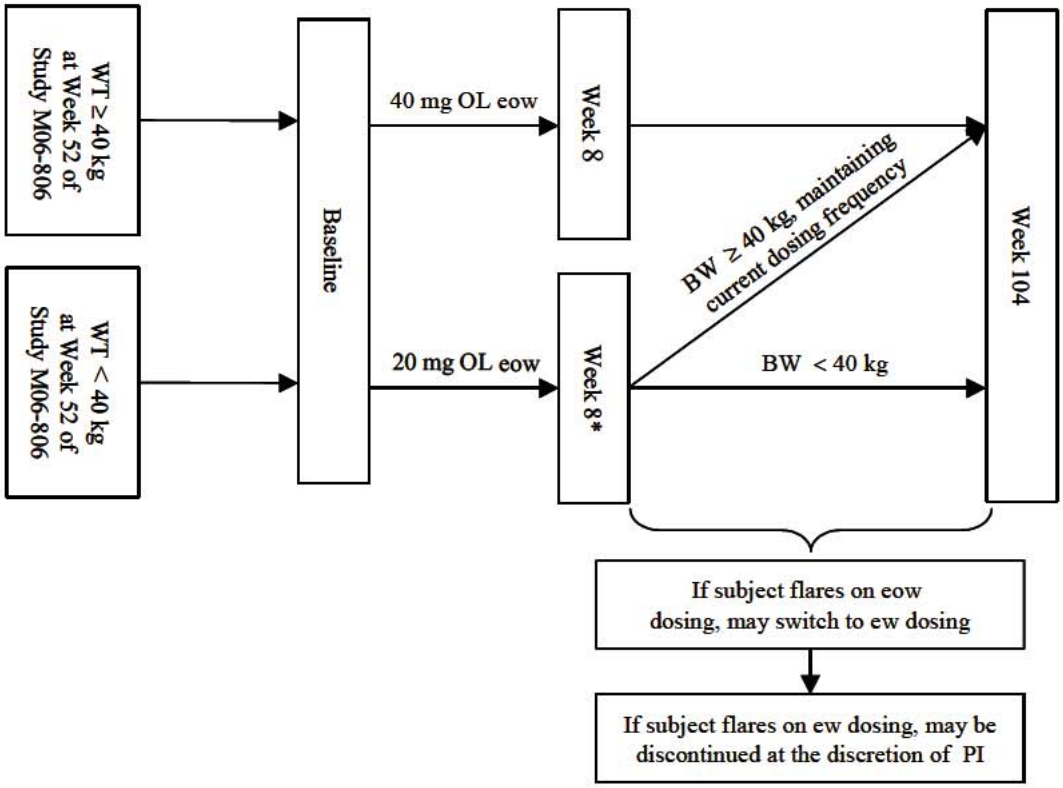
A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator

5.2 Selection of Study Population

Subjects will be evaluated to determine if they meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Protocol M06-806 through Week 52.

2. Subject must be a responder at Week 52 of Study M06-806.

3. If female, subjects who are sexually active and are of child-bearing potential should be practicing an approved method of birth control throughout the study and for 150 days after study drug administration. Examples of approved methods of birth control include the following:

   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD)
   - Oral, parenteral or intravaginal contraceptives
   - A vasectomized partner

4. Subject of legal age, parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, subject's parent, or legal guardian, as required, has had the opportunity to ask questions. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

5. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subject's diary.

6. If a subject of legal age, must be willing to actively store, administer, and accurately record study drug administration in the subject diary.

7. Subject is judged to be in acceptable medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding Crohn's disease study M06-806.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. For any reason, the subject is considered by the Investigator to be an unsuitable candidate for continuing therapy in the M06-807 study.

2. Subject has abnormal laboratory or other test results that in the opinion of the Investigator will make the subject unsuitable to participate in this study.

3. History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma−in-situ of the cervix.

4. History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active TB (receiving treatment or not receiving treatment). Ongoing severe infections such as sepsis and opportunistic infections will be exclusionary.

5. Subject with known, symptomatic obstructive strictures.

6. Subject who is planning surgical bowel resection at any time point while enrolled in the study.

7. Subject who has short bowel syndrome as determined by the Investigator.

8. Subject who is currently receiving total parenteral nutrition (TPN).

9. Subject who is unwilling to discontinue growth hormone prior to the first dose of open-label study drug at the Baseline visit of M06-807.

10. Female subject who is pregnant or currently breast-feeding.

11. Subject with a history of clinically significant drug or alcohol abuse in the last year.

12. Subject with a poorly controlled medical condition such as: uncontrolled diabetes, recurrent infections, unstable ischemic heart disease, moderate to severe heart failure, recent cerebrovascular accidents or any other condition which, in the

opinion of the Investigator or the Sponsor, will put the subject at risk by participation in the protocol.

13. Subject with any prior exposure to Tysabri (natalizumab).

14. Subject with a known hypersensitivity to the excipients of adalimumab as stated in the label.

15. Subject with a previous history of dysplasia of the gastrointestinal tract.

16. Subject is not in compliance with Section 5.2.3.

If there are any questions regarding inclusion and exclusion criteria and/or subject eligibility, contact the Abbott Laboratories Medical Monitor identified in Section 7.0.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication (including over-the-counter medicines such as aspirin) that the subject is receiving during the study must be recorded in source documents and on the appropriate case report form (CRF) along with the reason for use, dates of administration and dosages.

Any vaccine administered to the subject during the study should be listed as a concomitant medication. Subjects should continue on the recommended vaccination schedule; however, vaccinations with live vaccines are prohibited.

Any medications captured in the M06-806 CRF(s) which are ongoing will be transcribed onto the M06-807 source documents and CRF(s).

If there are any questions regarding prior or concomitant therapy (ies), contact the Abbott Laboratories Medical Monitor identified in Section 7.0

5.2.3.2 Concomitant Therapy

Adjustments of Crohn's related concomitant treatments, including Crohn's related antibiotics, are not allowed during the first 8 weeks of the M06-807 study, unless subject safety is at risk.

After Week 8, decreases in the dose or discontinuation of Crohn's related antibiotics or Crohn's related concomitant treatments are allowed according to the Investigator's medical judgment. These adjustments may be performed without prior discussion with the Abbott Medical Monitor. In addition, Subjects may be able to initiate or reinitiate Crohn's related treatments, except immunosuppressants, following eight (8) weeks of exposure to open-label adalimumab. Immunosuppressants may not be started or restarted during the study.

Setons are allowed as concomitant therapy in subjects with perianal fistulas. Their use should be documented on the concomitant medications page of the CRF.

Growth hormone must be discontinued prior to the first dose of open-label study drug and Subjects may not begin using it while participating in this study.

If a subject began to taper corticosteroids during the M06-806 study, they may continue this taper immediately upon enrollment into the M06-807 study. Beginning at Week 8, subjects who are not in flare may begin corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg	5 mg/week
	≤ 10 mg	2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Subjects who are in flare or who flare after they have reduced or completely tapered their dose of corticosteroid may have their corticosteroid dose increased or restarted, at the discretion of the Investigator.

5.2.3.3 Rescue Therapy

If the Investigator decides, during the study, that a subject requires rescue therapy other than that described in this protocol, the subject must be terminated from the study. If possible, questions regarding the use of rescue therapy should be discussed with the Medical Monitor prior to use.

5.2.3.4 Prohibited Therapy

Live vaccines must not be given concurrently while on study drug and for 70 days after the last dose of study drug.

Infliximab and growth hormone use are prohibited during the study. At the Baseline visit, any subject using Growth hormone must discontinue its use.

Tysabri (natalizumab), concurrent biological therapy, cyclosporine, tacrolimus, mycophenolate mofetil, Kineret® (anakinra), Orencia (abatacept), therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopies) and any investigational agent are prohibited during the study (see Appendix K).

Concurrent use of budesonide and prednisone (or equivalent) is prohibited.

Subjects with any prior exposure to Tysabri (natalizumab) will be excluded.

5.3 Efficacy, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Base-line	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104/ Early Term	Unscheduled visit	70-Day Follow-up Phone Call
Inclusion/exclusion criteria	X													
Informed consent	X													
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[e]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
CRP	X[a]				X		X		X			X		
ANA	X[a]			X								X		
Anti-dsDNA[f]	X[a]			X								X		
PCDAI	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
CDAI[g]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	
IMPACT III Questionnaire[h]	X[a]			X	X		X		X			X		
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X	X	X		

Activity	Base-line	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104/ Early Term	Unscheduled visit	70-Day Follow-up Phone Call
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI−CD)	X[a]	X	X	X	X	X	X	X	X	X	X	X		
X-ray for bone age	X[a]						X					X		
Serum bone markers	X[a]				X		X		X			X		
Adverse events[i]	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X	X		X[j]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the M06-806 study.
b. Performed on all females of child-bearing potential - Urine pregnancy test at all study visits.
c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.
d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.
e. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).
f. If an ANA result is positive, anti-dsDNA will be performed automatically.
g. For subjects who are age 13 or older at the M06-807 Baseline Visit, a CDAI will be completed at each visit.
h. For subjects who are age 10 or older at the M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, and 104/ET.
i. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).
j. If an unscheduled visit is performed to change the frequency of study drug from OL eow to OL ew, study drug may be dispensed.

5.3.1.1 Study Procedures

The M06-806 Week 52 visit will serve as the Baseline visit for the M06-807 study. The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate CRFs.

The visit window for all scheduled visits is ±7 days calculated from the Baseline visit of the M06-807 study.

Inclusion/Exclusion Criteria

A subject will be excluded from this study if he/she does not meet all inclusion criteria or meets any of the exclusion criteria of Protocol M06-807.

Informed Consent

A signed Informed Consent Form (ICF) will be obtained from a subject of legal age (in the state of residence) or from the parent or legal guardian (as appropriate)of a subject who is not of legal age before any study related procedures are undertaken or before any medications are discontinued for the purpose of this study. Additionally, an informed consent will be required from those subjects who were not of legal age at the onset of this study but become of legal age during the course of the study.

In keeping with each institution's IRB requirements, an Informed Assent may also be required from pediatric subjects. Pediatric subjects will be included in all discussions in order to obtain their signature on an assent form. Details about how informed consent will be obtained and documented are provided in Section 9.3.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subject's source.

Previous and Concomitant Medications

Changes in concomitant medications will be assessed at each study visit from Baseline through Week 104/ET visit. Concomitant medications that are taken prior to the first dose of study drug administration for this study will be captured in the subject's casebook from the previous study (M06-806). They will not be required to be captured in the subject's casebook of the M06-807 study unless they were ongoing at the Week 52 visit of the M06-806 study. Ongoing concomitant medications from the M06-806 study will be transcribed into the subject's M06-807 casebook.

Subjects of legal age or the parent or guardian (as appropriate) of subjects who are not of legal age will be provided with a medication log (see Appendix N) to record all medications the subject takes throughout the study. This log must be returned for review at every study visit.

Serum/Urine Pregnancy Test

All female subjects who are experiencing menses, are nearing sexual maturation (in the opinion of the Investigator), or who are of child-bearing potential, will undergo a urine pregnancy test at each visit. Urine pregnancy tests will be performed locally by designated study personnel. If a urine pregnancy test is positive, a serum pregnancy test must be performed by the central laboratory. If the serum pregnancy test is positive, the subject will be removed from the study.

A lactating or pregnant female will not be eligible for participation in this study.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, body temperature, weight and height will be obtained at each visit. All measurements will be recorded in metric units when applicable.

Weight measurements will be obtained using the same measuring instrument at each visit and measured with subjects wearing only undergarments. Height measurements will be

obtained using the same measuring equipment at each visit and performed on subjects with their shoes taken off.

Physical Examination

A physical examination will be performed at each visit. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam.[30] Fistulas will be classified as abdominal or perianal/anal.

Physical exam abnormalities (including fistulas and fissures) noted by the Investigator will be evaluated and documented on the corresponding source documents. Any new abnormalities or worsening of pre-existing conditions should be captured as AEs.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 2 at all study visits. Blood draws should be performed after questionnaires (PCDAI, IMPACT III Questionnaire, etc.) and vital sign determinations during a study visit, and before study drug administration.

ICON central laboratory will be utilized to process and provide results for the general laboratory tests. All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

ICON will provide instructions regarding the collection, processing and shipping of these samples.

Table 2. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry	Urinalysis[b]	Serum Bone Markers
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	Osteocalcin
Hemoglobin	Creatinine	Ketones	Bone-specific alkaline phosphatase (BSAP)
Red Blood Cell (RBC) count	Total bilirubin	pH	bone resorption (Ntx)
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein	
Neutrophils		Blood	
Bands		Glucose	
Lymphocytes	Serum glutamic-oxaloacetic transaminase (SGOT/AST)		
Monocytes			
Basophils			
Eosinophils	Alkaline phosphatase		
Platelet count (estimate not acceptable)	Sodium		
	Potassium		
	Calcium		
	Inorganic phosphorus		
	Uric acid		
	Cholesterol		
	Total protein		
	Glucose		
	Triglycerides		
	Albumin		

a. Basic hematology testing performed on instrumentation does not include band reporting. When Hematology results reflex to a Manual Differential, if there is a band result over 5, it is reported.

b. Microscopic urinalysis will be performed at any visits if dipstick UA is abnormal (protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

Immunologic Laboratory Assessments

CRP assessments will be performed at Baseline (Week 52 of the M06-806 Study), Weeks 24, 48, 72 and 104/ET. Antinuclear antibody (ANA) will be performed at Baseline (Week 52 of the M06-806 Study), Week 12, and Week 104/ET. If an ANA result is positive, anti-double-stranded DNA (anti-dsDNA) will be performed automatically. All CRP, ANA, anti-dsDNA will be performed by the central laboratory.

Erythrocyte Sedimentation Rate (ESR) assessments will be performed at all visits as indicated in Table 1. ESR assessments will be performed by the site's local laboratory.

Markers of Bone Metabolism

Serum markers of bone metabolism will be measured at Baseline (Week 52 of the M06−806 Study), Weeks 24, 48, 72 and 104/ET. The bone formation markers to be measured are osteocalcin, bone-specific alkaline phosphatase (BSAP), and bone resorption (Ntx).

Urinalysis

Urine will be assessed by dipstick at each visit (done locally). All results, including abnormalities, will be captured in source documentation and on the appropriate CRF. If, at any visit, the dipstick UA results are abnormal, the central lab will perform a microscopic urinalysis. Abnormal is defined as protein greater than a trace, blood greater than 5-10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL.

Pediatric Crohn's Disease Activity Index (PCDAI)

The PCDAI score will be calculated at each visit. When completing the PCDAI, the HCT, albumin, and ESR values will be utilized from the same study visit.

An example of the PCDAI is located in Appendix F. Instructions for completing the PCDAI score is located in Appendix G.

Crohn's Disease Activity Index (CDAI)

At each visit, a CDAI score will be calculated for subjects who are age 13 or older at the M06-807 Baseline Visit. The CDAI score will be calculated utilizing the subject diary and the HCT value from the same study visit. A copy of the CDAI subject diary is located in Appendix G.

When completing question five (5) ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured on the CDAI CRF page and calculated into the CDAI score.

The calculation of the CDAI score is in Appendix H.

IMPACT III Questionnaire

Subjects ≥ 10 years old at the Baseline visit of the M06-807 study will complete an IMPACT III questionnaire at Baseline, Weeks 12, 24, 48, 72, and 104/ET as indicated in Table 1. A copy of the questionnaire is located in Appendix J.

The IMPACT III will be recorded directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Outcomes

The Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalization Questionnaire and the Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) will be completed at each visit except the Unscheduled Visit (Appendix M, Appendix S).

The subject's parent or legal guardian will complete the WPAI directly onto the CRF. The completed CRF will be considered source documentation for this assessment.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained at Baseline (Week 52 of M06-806), Week 48, and Week 104/ET to determine changes in bone maturation as indicated in Table 1. Sites should use the Greulich and Pyle method for reading the x−ray.[31] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the CRF.

Anthropometric Evaluations

Height and weight obtained at each visit will be used by Abbott Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity (cm/yr) - mean height velocity for age and sex (cm/yr) / SD of the mean) for height.

Adverse Events

Adverse events will be assessed at every study visit from Baseline through Week 104 / Early Termination visit. Any AEs, which are ongoing in the M06-806 study, will be transcribed onto the M06-807 source documents and CRF(s)

For those subjects who complete the study or terminate early, a phone call will be made 70 days after the last dose of study drug to obtain follow-up information on any ongoing and any new AEs. See Section 6.0 and Appendix L for additional information.

Study Drug Administration

At each study visit, the subject or their trained designated friend, family member or health care professional will perform study drug injections under the supervision of a trained medical personnel to reinforce proper aseptic SC injection technique. Subjects or a trained designated friend, family member or health care professional will perform injections of study drug in the subject's home during weeks they are not in for scheduled clinic visits. Subjects may return to the study site for injections in between study visits if subject or a trained designated friend, family member or health care professional cannot inject the study medication.

Subjects will maintain a dosing diary for all study drug administered outside study visits, i.e., at home. In the diary, the date, initials of the person administering the study drug, time study drug is administered, kit number and the dose administered will be recorded. Subjects must return this diary and it will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study

drug administration will be recorded on source documents and appropriate drug accountability forms. A sample of the Subject Dosing Diary is presented in Appendix O.

At all office visits subjects should be observed after study drug administration, until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

The dosing dates, for all doses of study drug, should be calculated from the Baseline visit date. The Baseline visit date for this study is 364 ± 7 days from the Baseline Visit date of M06-806. A +/- 3 day window is allowable for scheduled study dosing dates.

For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the +/- 3 day window, please contact the Medical Monitor for additional instructions.

Randomization and Assignment of Subject Numbers

All subjects will be centrally registered using an IVRS. This is an open-label study; subjects will not be randomized. The telephone number and call in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous double-blind study (M06−806).

5.3.2 Drug Concentration Measurements

No drug concentration measurements will be obtained in this trial.

5.3.3 Efficacy Variables

Efficacy will be evaluated based on the proportion of subjects who maintain PCDAI clinical response at each visit. Clinical response is defined as PCDAI decrease ≥ 15 points from the M06-806 Baseline score.

Other measures of disease activity being assessed in this study will be summarized, including CDAI scores, IMPACT III scores, WPAI-CD Caregiver, z-score for height velocity, bone x-ray, serological markers of bone metabolism, and healthcare resource utilization (unscheduled outpatient visits).

5.3.4 Safety Variables

AEs, laboratory data, physical examinations and vital signs are the safety parameters and these will be assessed throughout the study.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject or subject's legal guardian requests withdrawal from the study.
- Selection criteria violation was noted after the subject started study drug, as determined by the Medical Monitor (see Sections 5.2.1 and 5.2.2).
- Introduction of prohibited medications or prohibited concomitant medication dosages as determined by the Medical Monitor.
- The subject is diagnosed with a malignancy except for localized non−melanoma skin cancer. Discontinuation for carcinoma in-situ is at the discretion of the Investigator.
- The subject is diagnosed with dysplasia of the gastrointestinal tract.
- A female subject who becomes pregnant.

If the subject prematurely discontinues study drug use, the procedures outlined for the Week 104/ET Visit must be completed within 2 weeks of the last dose of study drug, and

preferably prior to the initiation of another therapy. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

Subjects who prematurely discontinue from the study will not be replaced. The date of last dose and reason for premature discontinuation will be recorded in the source document and on the appropriate CRF.

5.4.2 Discontinuation of Entire Study

Abbott reserves the right to discontinue the study at any time and to remove all study materials from the site. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

5.4.3 Stopping Rules

An independent Data Monitoring Committee (DMC) will meet to discuss unblinded data from the study every six (6) months or at a frequency determined by the DMC and render their recommendation for either the continuation of the study or an amendment to the study. A Sponsor Steering Committee (SSC), composed of senior executives not directly participating in this study, will make final decisions based on DMC recommendations. In addition, an ad-hoc DMC meeting will be convened if either of the following criteria is met.

- The overall rate of SAEs, with an Investigator assessed causality of at least possibly related or higher, evaluated on a per subject-year basis, exceeds 0.45 (0.15 SAEs/subject every four months), or
- The overall rate of serious infectious SAEs evaluated on a per subject-year basis, exceeds 0.09 (.03 SAEs/subject every four months).

If either of these criteria is met, no new enrollment will occur until the DMC or the SSC makes their recommendations.

5.5 Treatments

5.5.1 Treatments Administered

All study drug will be provided as a SC injection solution in pre-filled syringes containing adalimumab 40 mg/0.8 mL or adalimumab 20 mg/0.8 mL.

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (Week 52 of M06-806) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may be increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight has increased from < 40 kg

to ≥ 40 kg from the study Baseline visit. The site will enter the subjects' body weight into the IVRS and the dose will be adjusted, if applicable.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3. Pre-filled syringes will be provided for this open-label clinical study.

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL or 20 mg/0.4 mL Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	Abbott

5.5.2.1 Packaging and Labeling

The following information will appear on the pre-filled syringe or carton labels:

- Sponsor identification
- Protocol number
- Drug identification
- Quantity of contents
- Storage conditions
- Dosing instructions
- Kit number
- Route of Administration
- Excipients
- Blank spaces to write the subject's identification number, initials, and date dispensed (as required)
- Finishing lot #
- Expiry Date (as required)

Two pre-filled syringes will be provided in a dosing kit carton (see Table 4). Detailed instructions and training for the administration of study supplies are provided in Appendix P.

Table 4. Study Drug Packaging and Administration

Open-label Pre-filled Syringes	
Open-label kit cartons containing two pre-filled syringes of adalimumab 40 mg/0.8 mL.	Open-label kit cartons containing two pre-filled syringes of adalimumab 20 mg/0.4 mL.

5.5.2.2 Storage and Disposition of Study Drug

Pre-filled syringes are to be stored protected from light at 2° to 8°C/ 36° to 46°F. DO NOT FREEZE. A storage temperature log is to be maintained at the site to document proper storage conditions. The refrigerator temperature must be recorded on every business day on a temperature log to record proper function. Malfunctions must be reported to the sponsor immediately. Study drug should be quarantined and not dispensed until Abbott GPRD or Abbott Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to Abbott Laboratories.

Investigational products are for investigational use only, and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study; all subjects will be receiving adalimumab.

All subjects will be centrally registered using an IVRS. The telephone number and call−in directions for the IVRS will be provided to each site. Subjects will keep their study subject number from the previous study (M06−806).

Study drug will be administered at the study visits summarized in Table 1 and detailed in Section 5.3.1.1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects who enroll into the study from blinded therapy in Study M06-806 will receive open-label therapy at a dose dependent on their body weight. Subjects who weigh ≥ 40 kg will receive 40 mg eow of adalimumab, while subjects who weigh < 40 kg will receive 20 mg eow of adalimumab. Beginning from Week 8, subjects who have a disease flare may be switched to ew treatment at the same dose of adalimumab received while on eow treatment.

Subjects who enroll into the study from open-label therapy in Study M06-806 will continue to receive the same dose they were receiving (i.e. 40 mg ew or 20 mg ew) at the Week 52 visit of the M06-806 study.

Subjects who develop a flare while receiving ew open-label therapy or have a PCDAI score ≥ 15 points when compared to their Baseline (the Week 52 visit of the M06-806 study) PCDAI score (regardless of study visit), may be discontinued from the study at the discretion of the Investigator.

The Baseline Visit date for this study should be 364 ± 7 days from Baseline Visit date of M06-806 study. All clinic visits for the subject should be scheduled on the same day of the as the Baseline visit for this study. For home administration of drug, subjects will be instructed to inject study drug on the same day of the week as their Baseline visit day. Subjects must inject within a +/-3 day window of this day. If the subject is out of the dosing window, the Medical Monitor should be contacted to determine the timing of the next dose. The subject must record all dosing information on the subject dosing diary (Appendix O).

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will administer study drug only to subjects enrolled in the study.

In order to document compliance with the treatment regimen, all pre-filled syringes will be counted and documented in source documents and on the appropriate drug accountability form.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts from the drug depot. This will be documented by signing and dating the Proof of Receipt (POR) or similar document. The original POR or similar document will be kept in the site files as a record of what was received. An accurate running inventory of study drug will be kept by the site, and will include the kit number, lot number(s), the number of pre-filled syringes dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Clinical Research Associate (CRA) throughout the study and at the site close-out visit. All unused pre-filled syringes will be inventoried and returned to an identified vendor for disposal as designated by Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with instructions provided by the CRA, will also be included in the Returned Goods for disposal shipment. A sample Drug Accountability Form is included in Appendix R. A copy of the Drug Accountability Disposal Form, in accordance with instructions provided by the CRA, will also be included in the Pharmacy Binder provided to the site.

All used (expelled) pre-filled syringes will be inventoried by the site and verified by the CRA. The used syringes will be discarded on site, using appropriate biohazard precautions. CRAs and site staff will complete study drug accountability via study drug logs, source documents, verification of empty used syringe kit boxes, subject diaries and by visually counting the syringes in the sharp's container whenever possible. Used sharp's containers should never be opened. Each subject will be given their own sharps

disposal container to store expelled syringes. Sharps containers should be returned by the subject at each visit, for accountability and compliance purposes. New containers will be issued to subjects as necessary. Once the CRA has verified drug accountability at the site, the site staff and CRA will sign off that the expelled pre-filled syringes have been destroyed.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical study was chosen to demonstrate adalimumab as an effective therapy for maintaining clinical response in pediatric subjects with CD and to gather long-term safety and tolerability data in this subject population.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in pediatric subjects with Crohn's disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with CD who have participated in and successfully completed Protocol M06-806 through Week 52 and who meet all of the inclusion and none of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The results of the pivotal adalimumab adult CD maintenance trial M02-404, in conjunction with results from adalimumab CD Study M02-433, support a maintenance dose of adalimumab 40 mg eow. Data also suggest that patients who lose response to adalimumab at 40 mg eow can be dose-escalated to 40 mg weekly with the potential of regaining clinical response. The proposed dosing regimen for Study M06-807 was developed using an analogous approach as that studied in the adult CD population.

Population pharmacokinetic modeling of serum adalimumab concentration data from pediatric subjects with JRA was used to identify doses to be evaluated in the current study in children with CD. A model based on the JRA population was chosen because the body weight range will closely parallel that in a juvenile CD population. Escalation to weekly dosing will provide average adalimumab concentrations at steady state about twice that observed with every other week dosing. However, these concentrations are within the range of systemic exposures that were safely studied in adult subjects with CD.

6.0 Adverse Events

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to study drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to study drug, the Investigator must provide another cause of event. For AEs to be considered sporadic, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded in source documentation and on the appropriate CRF page.

All AEs will be followed to a satisfactory conclusion.

6.1 Definitions

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to Abbott as an SAE within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, will have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that will have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

6.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

6.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and an other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the study drug and an other cause of event is equally or less likely compared to the potential relationship to study drug.

Probably Not Related	An AE has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

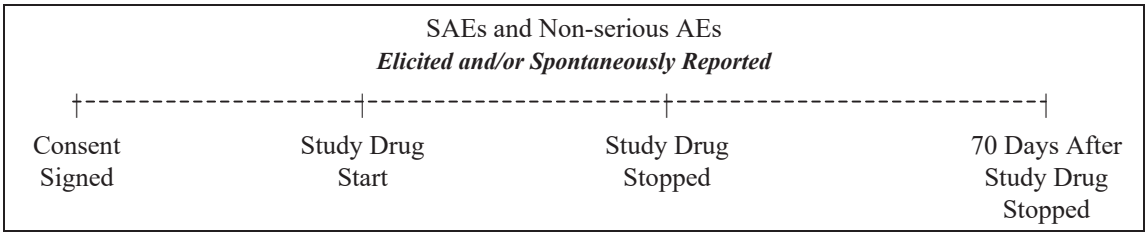
If an Investigator's opinion of possibly, probably not, or not related to study drug for an SAE is given, an alternative cause of the event must be provided by the Investigator for the SAE.

6.4 Adverse Event Collection Period

All AEs reported from the time of informed consent until 5 half-lives (70 days), following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, SAEs will be collected from the time the subject or parent/legal guardian has signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of an SAE, whether related to study drug or not, the Investigator will notify Abbott by faxing the appropriate SAE forms to one of the following people within 24 hours of the site being made aware of the SAE. Additionally, if follow-up information is received, it must also be reported to Abbott within 24 hours of being made aware of the information.

For sites located within North America:

SAE Support Hotline

For sites located outside North America:

For questions regarding SAEs, please contact:

6.5.1 Collection of Data Regarding Known Manifestations of the Disease Under Study

Flare, of Crohn's disease events per study definition, are not required to be captured as AEs, but may be captured per Investigator discretion. Additionally, CD pre-existing conditions will not be captured as AEs unless the condition has worsened or is considered clinically significant in the opinion of the Investigator.

6.6 Pregnancy

Abbott Laboratories must be notified within 1 working day of a site's learning if a female subject becomes pregnant during the study or within 150 days of receiving the last dose of study drug (see Section 6.5 for contact information).

Females who become pregnant during the study will be discontinued from study drug as described in Section 5.4. Data regarding the outcome of any pregnancy occurring in a study subject will be collected. Upon notification of a pregnancy Abbott will forward a form to the site, for the Investigator to complete and send back to Abbott. A second form will also be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also need to be completed and sent back to Abbott.

To monitor outcomes of pregnant women exposed to adalimumab, a pregnancy registry has been established for the United States. Physicians in the United States are encouraged to register subjects by calling [redacted] and/or provide this information to the subject.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or a spontaneous abortion, stillbirth or congenital anomaly is considered a SAE, and must be reported to the sponsor with 24 hours of the site learning of the event.

7.0 Protocol Deviations

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the following Abbott representative:

[redacted]

For purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though they did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn

- Subject who received wrong treatment or incorrect dose
- Subject who received excluded concomitant treatment

Such contact must be made as soon as possible to permit a review by Abbott to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Analyzable Population

Efficacy analyses will be conducted in the intent-to-treat (ITT) population, which is defined as all subjects who received at least one dose of adalimumab in Study M06-807. In order to evaluate the impact of major protocol violations / deviations on the results of the study, additional analyses may be performed on the per-protocol population, which excludes all subjects with major protocol deviations. The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807.

8.1.2 Planned Methods of Statistical Analysis

All statistical analyses are to be performed descriptively. Descriptive summary statistics will be provided for the demographic and baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

8.1.2.1 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind study M06-806).

8.1.2.2 Primary Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subject's last non-missing, post-baseline value (i.e., post-Week 52 M06-806 double-blind value) will be carried forward to the last visit.

8.1.3 Other Analyses

The primary endpoint will be analyzed for the following subgroups in the ITT population.

- Sex [Male, Female]
- Age [< 13 years, ≥ 13 years]
- Ethnicity [White, Non-white]
- Weight [< 40 kg, ≥ 40 kg]
- Prior infliximab use [No, Yes]
- Baseline CRP [< 1.0 mg/dL, ≥ 1.0 mg/dL]
- Concomitant use of immunosuppressants and/or oral corticosteroids [No, Yes]

8.1.4 Safety Analyses

Safety analyses will be based on the safety population. Treatment-emergent, and post−treatment AEs will be summarized. An overview of treatment-emergent AEs including AEs of special interest, such as AEs leading to death and AEs leading to premature discontinuation, AEs by (MedDRA® version 10.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized. Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study drug and within 70 days after the last dose of the study drug.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as probably related.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported AEs will be included in the AE data listings.

For laboratory parameters, the normal range of the analyzing laboratory will be used and all values outside the normal range will be 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 will be calculated for the continuous clinical laboratory parameters.

Shift tables will be 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 will be flagged in reference to the normal range (low, normal, high) and also categorized as clinically non-significant (CTC grade < 3) or clinically significant (CTC grade ≥ 3). Further details will be provided in the SAP.

8.1.5 Interim Analysis

There are no planned interim analyses.

8.2 Determination of Sample Size

Subjects who successfully completed Study M06-806 through Week 52 may be eligible to participate in this study. It is expected that approximately 70% (130) of subjects from the M06-806 study will enroll in this study.

8.3 Randomization Methods

All subjects will be centrally registered using an IVRS. This is an open-label study; therefore, subjects will not be randomized before the study is initiated, the telephone

number and call in directions for the IVRS will be provided to each site. Subjects will keep their subject number from the previous study (M06-806).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. A list of the documents required prior to initiation of the study can be found in Appendix B.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects, unless otherwise submitted by the sponsor. Written documentation of the submission to the IEC/IRB should also be provided to Abbott.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical trial conduct, and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix C.

9.3 Subject Information and Consent

Prior to any study-related procedures or discontinuation of any medications for this study, the Investigator or his/her representative will explain the nature of the study to the subject of legal age (in the state of residence) or to the parent or legal guardian (as appropriate)of a subject who is not of legal age and answer all questions regarding this study. Subjects will be included in all discussions.

The ICF will be reviewed, signed and dated by the subject of legal age (in the state of residence) or by the parent or legal guardian (as appropriate) of a subject who is not of legal age, and the person who administered the informed consent. If a subject who was not of legal age at the onset of this study becomes of legal age during the course of the study, an informed consent will need to be obtained at that time. Additionally, in keeping with each institution's IRB requirements an Informed Assent will also be obtained from the subject, as required.

A copy of the signed ICF and Assent Form will be given to the subject and the subject's parent/legal guardian. The original signed ICF and Assent Form will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

If an updated informed consent is approved after a subject has completed or terminated early from the study, but is within the 70-day follow-up window, the subject will not be required to return to the site for the purposes of signing the updated ICF. The subject of legal age, parent or legal guardian (as appropriate) should be contacted regarding any changes and the documentation of the contact should be present in the subject's source.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

The IMPACT III questionnaire and the WPAI questionnaire will be recorded directly on the CRF(s) by the subject, parent or legal guardian (as appropriate) and these CRFs will be considered source data.

10.2 Case Report Forms

Case report forms will be supplied by Abbott. These forms will be used to transmit information collected during the study to Abbott and regulatory authorities, as applicable. Case report forms must be completed for each subject enrolled in this study. All case report forms must be legible and completed in indelible black ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision. All revisions must be initialed and dated by the Investigator or his/her representative. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) should accompany the change. All information written on the case report forms must also be reflected in the subject source documents with the exception of the case report forms discussed above in Section 10.1.

The Principal Investigator will review the case report forms for completeness and accuracy and sign and date each set of case report forms where indicated. The case report forms will be reviewed periodically for completeness, legibility and acceptability by Abbott personnel (or their representatives). Abbott (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

Once the original case report form has been removed from the site, all changes must be made via the appropriate change form specified by Abbott. The Principal Investigator will review the change form for completeness and accuracy and sign and date the change form where indicated.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigator's meeting will be held with Abbott personnel, the Investigators and their study coordinators, the CRO's project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF and Subject Diary completion, and specimen collection methods. In addition to or instead of the Investigator's meeting, the study personnel at each site may be trained on the study procedures by a CRA at a study initiation visit and will be given a CRF completion workbook for reference.

The CRAs will monitor at each site throughout the study. One hundred percent (100%) source document review will be performed against entries on the CRF and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

All data hand entered in the database will be verified by a double-key entry procedure at Abbott. Any discrepancies will be reviewed against the hard copy CRF and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values. Any necessary

corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

Routine hematology, serum chemistry, and serology will be conducted using a central laboratory. ESR analysis will be done at a local lab designated by the site. The data from these analyses will be electronically transferred from the central laboratory to the study database. Urinalysis will be completed locally. If a microscopic urinalysis is necessary, this testing will be conducted using the central laboratory. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

Sites will provide Abbott (or designate) with laboratory certifications (CAP and CLIA), CV of local lab director, and reference ranges for each local lab used. The full name, address, phone number, and fax number for each local lab will also be included.

12.0 Use of Information and Publication

12.1 Use of Information

All information concerning adalimumab and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of adalimumab. This information may be disclosed as deemed necessary by Abbott Laboratories to other clinical Investigators, other pharmaceutical companies, to the FDA, and to other government agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide Abbott Laboratories with complete test results and all

data developed in this study and to provide direct access to source data/documents for study- related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by Abbott.

12.2 Publication

All information concerning adalimumab and Abbott Laboratories' operations, such as patent application, formulas, manufacturing processes, basic scientific data or formulation information supplied by Abbott Laboratories which have not been previously published are considered confidential by Abbott Laboratories and shall remain the sole property of Abbott Laboratories. The Investigator agrees to use this information only to perform this study and will not use it for other purposes including publications and presentations without Abbott Laboratories' written consent.

It is understood by the Investigator that the information developed in the clinical trial will be used by Abbott Laboratories in connection with the development of adalimumab and, therefore, may be disclosed as required to other clinical Investigators, other pharmaceutical companies, to the U.S. FDA and to other regulatory agencies. It is understood that there is an obligation to provide Abbott Laboratories with complete test results and all data resulting from this study and to provide direct access to source data/documents for study related monitoring, audits, IEC/IRB review, and regulatory inspection.

12.3 Internet Sites

Information regarding this study may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description of the study, study objectives, doses, accruing Investigators (upon their approval) and number of subjects to be enrolled.

13.0 Completion of the Study

The Investigator will conduct this study in compliance with the protocol, and will complete the study within the timeframe specified in the contract between the Investigator and Abbott. Continuation of the study beyond this time must be mutually agreed upon in writing by both the Investigator and Abbott. The Investigator will provide a summary of the study's outcome to the IEC/IRB following conclusion of the study, and will forward a copy of this summary to Abbott or their designee.

Abbott may terminate this study prematurely, either in its entirety or at individual sites, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott a reasonable time in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Abbott terminates the study for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Abbott will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The Investigator will retain all essential documents until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of follow-up contact, whichever is longer.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for Humira.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title: 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

Protocol Date: 11 January 2008

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CD	Crohn's disease
CDC	Center for Disease Control
CNS	Central Nervous Systems
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
eow	Every other week
ESR	Erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
ew	Every week
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
ICF	Informed Consent Form
IRB	Institutional Review Board

ITT	Intent-to Treat
IVRS	Interactive Voice Response System
JRA	Juvenile Rheumatoid Arthritis
LOCF	Last Observation Carried Forward
MTX	Methotrexate
Ntx	N−telopeptide
OL	Open-Label
PCDAI	Pediatric Crohn's Disease Activity Index
POR	Proof of Receipt
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SSC	Sponsor Steering Committee
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-CD	Work Productivity and Activity Impairment Questionnaire: Crohn's Disease

Appendix B. Documents Required Prior to Initiation of the Study

As sponsor of a clinical trial, Abbott has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the Investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical trial, the Investigator will be asked to provide the following documentation.

1. A signed and dated Investigator's agreement page for the study.

2. A signed and dated Form FDA 1572 certifying the Investigator's agreement to comply with the appropriate regulations governing the conduct of the study.

3. A current *curriculum vita* of the Investigator. If subinvestigators will participate in the study, *curriculum vita* for each.

4. Requirements for the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

   - A copy of the signed and dated letter of approval of the IEC/IRB. The letter must specify that both the protocol and informed consent form were approved (unless separate documentation that the informed consent was approved is provided).
   - A dated list containing the names and affiliations of the members of the IEC/IRB, or the institution's General Assurance Number.
   - If the Investigator and/or subinvestigator is a member of the IEC/IRB, a letter stating that he/she did not participate in the review or approval of the protocol or informed consent form.

5. A specimen copy of the IEC/IRB-approved informed consent document to be used in the study.

6. A list of reference ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.

7. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

8. Financial Disclosure forms must be completed by each Investigator and all Subinvestigators identified on the Form FDA 1572. A Financial Disclosure, EU consent, is required to be completed for each Investigator and/or Subinvestigator who is a resident of the European Union.

Appendix C. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (Abbott), summarizing the Investigator's qualifications for the study and his/her willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the study(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying Abbott, except when necessary to protect the safety, rights, or welfare of subjects.

2. To personally conduct or supervise the described investigation(s).

3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.

4. To report to Abbott adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.

6. To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the study and make those records available for inspection by representatives of Abbott, the IEC/IRB and/or the appropriate regulatory agency, and to retain all study-related documents until notification from Abbott. The Investigator must notify Abbott when they are no longer able to retain the study related documents.

8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from Abbott to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10. To comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix D. CDC Treatment of Tuberculosis Infection (Preventive Therapy)

When taken as prescribed, isoniazid therapy is highly effective in preventing latent tuberculosis (TB) infection from progressing to TB disease.

Who should receive preventive therapy?

The following persons should be given high priority for preventive therapy if they have positive skin test results, regardless of their age:

1. Persons with 5 mm induration on their PPD who will receive a TNF inhibitor,
2. Persons known to have or suspected of having HIV infection (5 mm or greater of induration),
3. Persons who have been in close contact with someone who has infectious TB disease (5 mm or greater),
4. Persons whose skin test results converted from negative to positive within the past 2 years (10 mm or greater),
5. Persons with abnormal chest radiographs who have never been treated for TB or who have been inadequately treated for TB (5 mm or greater),
6. Persons who have injected drugs and who are HIV seronegative (10 mm or greater), and
7. Persons with organ transplants and other immunosuppressed subjects (5mm or greater),
8. Persons who have medical conditions that increase the risk for TB (10 mm or greater). These conditions include diabetes mellitus, gastrectomy, some hematologic and reticuloendothelial diseases, and end-stage renal disease, silicosis, and body weight that is 10% or more below ideal.

In addition, in the absence of any of the above risk factors, persons in the following groups should be evaluated for preventive therapy if their reaction to the tuberculin skin test is 10 mm or greater:

1. Foreign-born persons from countries where TB is common;
2. Medically underserved, low-income populations; and
3. Residents of long-term care facilities.

In addition, staff of facilities in which a person with infectious TB disease would pose a risk to large numbers of susceptible persons (e.g., health care facilities, correctional facilities, and nursing homes) should be evaluated for preventive therapy if they have a positive skin test result.

Persons who have a positive reaction to the tuberculin skin test should not be given preventive therapy until the possibility of TB disease has been ruled out. In addition, persons who are being considered for preventive therapy should be evaluated for medical contraindications, such as:

1. Previous isoniazid-associated hepatic injury,
2. History of severe adverse reactions to isoniazid, and;
3. Acute or active liver disease.

Also, special precautions should be taken for some persons who are receiving preventive therapy.

Precautions are indicated for:

1. Persons who are older than 35,
2. Persons who abuse alcohol,
3. Pregnant women,
4. Persons with chronic liver disease,
5. Persons with peripheral neuropathy, and
6. Persons who in the past have stopped using isoniazid because of adverse effects.

Regimens for Preventive Therapy

The usual preventive therapy regimen is 9 months of daily isoniazid, in a dosage of 5 milligrams per kilogram of body weight. The maximum daily dose is 300 milligrams. HIV-infected persons should receive 9 months of preventive therapy. An alternative regimen for adults is 4 months of rifampin.

For persons with a strain of *M. tuberculosis* that is resistant to isoniazid but susceptible to rifampin, CDC recommends the use of rifampin alone for 4 months for preventive therapy.

Adverse Reactions

The major toxic effect of isoniazid is hepatitis. The risk for hepatitis increases with alcohol consumption. Isoniazid may also cause peripheral neuropathy. Persons at risk for neuropathy—for example, persons who abuse alcohol and persons with diabetes—should be given pyridoxine, or vitamin B-6, in conjunction with isoniazid therapy.

Subjects should be educated about the signs and symptoms of toxicity to isoniazid, and they should be monitored monthly by appropriately trained personnel. No more than a

1 month supply of medicine should be dispensed at any visit. If signs or symptoms of toxicity appear, isoniazid should be stopped immediately, and the subject reevaluated. Subjects should not be given isoniazid preventive therapy if they cannot be monitored monthly.

Appendix E. Non-Drug Materials Provided to the Study Site(s)

Study sites will receive the following supplies prior to or during the study:

Tote Bags

Cooler

Sharps Containers

Ice Packs

CDAI subject diary

Dosing Diaries

Subject Medication Log

Self Injection Instructions

Appendix F. Pediatric Crohn's Disease Activity Index (PCDAI)

							Score
1.	Abdominal pain rating						
	- None		= 0 p				
	- Mild - Brief, does not interfere with activities		= 5 p				
	- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p				
2.	Stools (per day)						
	- 0–1 liquid stools, no blood		= 0 p				
	- Up to 2 semi-formed with small blood, or 2–5 liquid		= 5 p				
	- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p				
3.	Patient Functioning, General Well-Being						
	- No limitation of activities, well		= 0 p				
	- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p				
	- Frequent limitation of activity, very poor		= 10 p				
LABORATORY							**Score**
4.	HCT: Male and female ≤10 years:			Male 11–14 years:			
		≥33	= 0 p		≥35	= 0 p	
		28-32	= 2.5 p		30-34	= 2.5 p	
		<28	= 5 p		<30	= 5 p	
	Female 11–19 years:	≥34	= 0 p	Male 15–19 years:	≥37	= 0 p	
		29-33	= 2.5 p		32-36	= 2.5 p	
		<29	= 5 p		<32	= 5 p	
5.	ESR (mm/hr)	<20	= 0 p				
		20-50	= 2.5 p				
		>50	= 5 p				
6.	Albumin (g/dL)	≥3.5	= 0 p				
		3.1-3.4	= 5 p				
		≤3.0	= 10 p				

EXAMINATION			**Score**
7. Weight	- Weight gain or voluntary weight stable/loss	= 0 p	
	- Involuntary weight stable, weight loss 1–9%	= 5 p	
	- Weight loss ≥10%	= 10 p	
8. Height			
	Height velocity ≥ -1SD	= 0 p	
	Height velocity < -1SD, > -2SD	= 5 p	
	Height velocity ≤ -2SD	= 10 p	
9. Abdomen	- No tenderness, no mass	= 0 p	
	- Tenderness, or mass without tenderness	= 5 p	
	- Tenderness, involuntary guarding, definite mass	= 10 p	
10. Perirectal disease	- None, asymptomatic tags	= 0 p	
	- 1–2 indolent fistula, scant drainage, no tenderness	= 5 p	
	- Active fistula, drainage, tenderness, or abscess	= 10 p	
11. Extra-intestinal Manifestations			
(Fever ≥38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)			
- None		= 0 p	
- One		= 5 p	
- ≥Two		= 10 p	
TOTAL SCORE	**Pediatric Crohn's Disease Activity Index (PCDAI)**		

Appendix G. PCDAI User's Guide and Guideline for Reference Weight and Reference Height

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with Crohn's disease participating in clinical trials.

History

All calculations are based upon a one-week (7 day) history recall of symptoms. The history recall should be solicited from the subject and/or caregiver.

Item 1. Abdominal pain

The descriptions in the PCDAI of "mild" and "moderate/severe" should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, subject should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

Item 2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the subject as having blood in the stool or not.

If there is **no blood** in the stool, score as follows:

Formed stools or up to 1 loose stool daily = 0
2-5 liquid or very loose stools on 1 or more days = 5
6 or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If **blood** is present in the stool on any day during the past week, score as follows:

Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

Item 3. Subject functioning, general well-being

If there is variation during the week, subject should be scored according to the most significant limitation of activity, even if it occurs during only one day of the week, as long as it is likely due to Crohn's disease and not to an intercurrent illness.

Item 4. Hematocrit

Hematocrit values should be rounded to a whole number prior to completing the calculation. Numbers that fall between the range of 0.1-0.4 must be rounded down. Numbers that fall between the range of 0.5-0.9 must be rounded up.

Physical Examination

Item 7. Weight (The intent is to assess the ability to normally maintain or gain weight)

Reference weight to be used for calculation of weight gain/loss during the study:

From Baseline to Week 104: use weight from previous visit

Voluntary weight stable/loss means subject maintaining or losing weight on purpose.

Involuntary weight stable means subject wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Weight from previous visit} - \text{Current weight}}{\text{Weight from previous visit}} \times 100 = \%\ \text{weight loss}$$

Item 8. Height

Reference height for calculation of height velocity

- From Baseline to Week 24, use height from 6 months prior to Baseline
- From Week 24 to Week 52, use height from Baseline visit
- From Week 52 to Week 72, use height from Week 24
- From post Week 72, use height from Week 52

The intent is to assess the normalcy vs. impairment of the subject's recent linear growth. Note that post-pubertal subjects will score 0 points. For subjects still growing, there are two options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

1. Height velocity (cm/year), the most sensitive parameter, should be calculated as below:

   $$\frac{\text{Present height} - \text{Appropriate height measurement (from above)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

   Using height velocity chart below, determine centile for height velocity.

2. Scoring for the PCDAI:

   a. Velocity less than "Minus 2 SD" scores 10 points.

   b. Velocity between "Minus 2 SD" and "Minus 1 SD" scores 5 points.

   c. Velocity greater than "Minus 1 SD" scores zero points.

* Please note that subjects should score zero points if a subject is a female above 14.5 years of age or a male above 17.5 years of age.

Height Velocity Reference Values for Calculating the PCDAI (Males)

	Height Velocity in cm per year (Males)		
Age (years)	Minus 2SD	Minus 1SD	Mean
2.5	5.7	7.0	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6.0	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6.0
7	4.2	5.0	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4.0	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

Height Velocity Reference Values for Calculating the PCDAI (Females)

	Height Velocity in cm per year (Females)		
Age (years)	Minus 2SD	Minus 1SD	Mean
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6.0
7.5	4.3	5.1	5.9
8	4.2	5.0	5.8
8.5	4.2	4.9	5.7
9	4.2	5.0	5.8
9.5	4.3	5.0	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0.0	0.5	1.0

Appendix H. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0=none, 1=mild, 2=moderate, 3=severe	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0=generally well, 1=slightly underpar, 2=poor, 3=very poor, 4=terrible	__+___+___+___+___+___+___+___=___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: **Check all items that apply:** □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil / Imodium / Loperamide /opiates for diarrhea 0=no, 1=yes	_____	X	30	
6. Abdominal mass 0=none, 2=questionable, 5=defined	_____	X	10	
7. Hematocrit: _____	Male: (47 - hematocrit) = Female: (42 - hematocrit) = Subtotal _____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height: __ __ __ . __ (kg)	100 x [1 - (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

* Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

* Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of .1-.4 must be rounded down. Numbers that fall between the range of .5-.9 must be rounded up.

Appendix I. Subject CDAI Diary

Enter all values legibly using a black ballpoint pen. **Add item requested for each day.**	**Crohn's Disease Activity Index Subject Diary Card**						
	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___	Day Date___
Number (total) of liquid or very soft stools per day.							
Daily abdominal pain rating. (0=none, 1=mild, 2=moderate, 3=severe)							
Daily rating of general well being. (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)							

Subject Initials:_____ Subject's Signature:_____

Investigator or Designee's Signature:_____

Appendix J. IMPACT III Questionnaire

INSTRUCTIONS

Below you will find a questionnaire containing 35 questions for children who have inflammatory bowel disease (Crohn's disease or ulcerative colitis). The questions are about your life with inflammatory bowel disease. Some questions deal with, for example, pains you may suffer from, others are about feelings or worries you may have.

After each question you will see boxes above five possible answers. Please put **a cross in the box above the answer that best fits your answer**.

First an example:

The question is: How afraid are you of tigers?

☐	☐	☐	☒	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

So, this person is **afraid** of tigers.

☐	☒	☐	☐	☐
Not at all afraid	A little afraid	Quite afraid	Afraid	Very much afraid

This person is **a little afraid** of tigers.

Please answer **all the questions**! If you do not understand a question, ask someone for help.

Good luck with filling in the questionnaire and....many thanks in advance for your efforts!

Question 1. How much has your stomach been hurting you in the past two weeks?

☐	☐	☐	☐	☐
Not at all	Hardly hurting at all	Hurting somewhat	Hurting quite a bit	Hurting very much

Question 2. Taking medicines or tablets bothers you

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 3. How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 4. How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 5. How much does it bother you that you have an illness that does not just go away?

☐	☐	☐	☐	☐
Not at all	Hardly bothers at all	Bothers somewhat	Bothers quite a bit	Bothers very much

Question 6. How much energy did you have during the past two weeks?

☐	☐	☐	☐	☐
Very much energy	Quite a bit of energy	Some energy	A little energy	No energy at all

Question 7. How do you feel about your weight?

☐	☐	☐	☐	☐
I feel great about my weight	I feel good about my weight	I don't feel good or bad about my weight	I feel bad about my weight	I feel awful about my weight

Question 8. How has your inflammatory bowel disease affected your family?

☐	☐	☐	☐	☐
The effect has been great	The effect has been good	It has not affected our family	The effect has been bad	The effect has been awful

Question 9. How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 10. How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 11. How often do you worry about health problems you might have in the future?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 12. How often do you think it is unfair that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 13. During the past two weeks, were you ever angry that you have inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 14. Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 15. How do you feel about the way you look?

☐	☐	☐	☐	☐
I think I look great	I think I look good	I don't think I look good or bad	I think I look bad	I think I look awful

Question 16. Are you embarrassed because of your bowel condition?

☐	☐	☐	☐	☐
Not at all	Hardly embarrassed at all	Embarrassed somewhat	Embarrassed quite a bit	Embarrassed very much

Question 17. Did you have fun during the past two weeks?

☐	☐	☐	☐	☐
Very often	Often	Sometimes	Rarely	Never

Question 18. Is it harder to make friends because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all harder	A little harder	Quite a bit harder	Much harder	Very much harder

Question 19. How often do you worry about your stool (bowel movement) containing blood?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 20. Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?

☐	☐	☐	☐	☐
Not at all worried	Hardly worried at all	Worried somewhat	Worried quite a bit	Worried very much

Question 21. How often did you feel sick to your stomach in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 22. How do you feel about the tests you have to go through?

☐	☐	☐	☐	☐
I do not mind them at all	I mind them a tiny bit	I mind them a little	I mind them a lot	I hate them

Question 23. Do other children bully you or leave you out of things because of your inflammatory bowel disease or its treatment?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 24. How often do you worry about having an operation?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 25. In the past two weeks how often were you afraid you may have an accident or not get to the toilet in time?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 26. Do you try to keep your inflammatory bowel disease a secret from other people?

☐	☐	☐	☐	☐
No, I do not try at all	I don't try much	I try a little	I try hard	Yes, I try very hard

Question 27. Does your inflammatory bowel disease make it difficult to travel or go on a holiday?

☐	☐	☐	☐	☐
No, not difficult	A little difficult	Quite difficult	Very difficult	Yes, extremely difficult

Question 28. How did you feel during the past two weeks?

☐	☐	☐	☐	☐
Great	Good	Not good or bad	Bad	Awful

Question 29. Are you happy with your life?

☐	☐	☐	☐	☐
Yes, very happy	Happy	Not happy or unhappy	Unhappy	Very unhappy

Question 30. Do you feel there is someone you can talk to about your inflammatory bowel disease?

☐	☐	☐	☐	☐
Always	Often	Sometimes	Rarely	Never

Question 31. How often did you have to pass gas in the past two weeks?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Very often

Question 32. How tired have you felt in the past two weeks?

☐	☐	☐	☐	☐
Not at all tired	A little tired	Quite tired	Tired	Very tired

Question 33. How do you feel about your height?

☐	☐	☐	☐	☐
I feel great about my height	I feel good about my height	I don't feel good or bad about my height	I feel bad about my height	I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐	☐	☐	☐	☐
Never	Rarely	Sometimes	Often	Always

Question 35. In the past two weeks how often were you able to go to school? (If you are in the middle of a school break or the summer holidays, answer as if school was on)

☐	☐	☐	☐	☐
Always	Most days	Half the days	A few days	Never

End of questionnaire

This completes the questionnaire. Do you have anything else to add which you feel is important about having inflammatory bowel disease, or do you have any other remarks? Please write them below.

_____

_____

_____

Appendix K. Excluded Medications

Cyclosporine

Tacrolimus

Therapeutic enemas and suppositories (not including those done in conjunction with routine colonoscopy)

Live vaccines

The combination of budesonide and prednisone (or equivalent)

Infliximab

Mycophenolate mofetil (MMF or CellCept®)

Growth Hormone

Kineret® (anakinra)

Tysabri (natalizumab)

Orencia (abatacept)

Concurrent biologic therapy

Any investigational agent

Any previous anti-TNF medication except infliximab before the study (including adalimumab).

Appendix L. Day 70 Phone Call

Site Name / Number: _____

Subject Number:_____

Subject Initials:_____

Please contact all Subjects 70 days following drug discontinuation.

Date of Call: _____

☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).

☐ No Events Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF to be submitted to data management. (Please report all SAEs to Abbott within 24 hours of being made aware of the event. Follow-up information must also be reported within 24 hours of being made aware of the information.).

If events are listed above, your monitor will review and retrieve the appropriate CRF pages during their next visit. Please fax this form to Abbott at [redacted]

Appendix M. Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations

1. Since the last study visit has the subject had any physician/health care visits for their Crohn's disease other than the protocol required visits?

   Yes ___
   No ___

If yes provide the following:

I. Since the last visit, has the subject been seen by a physician for their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

II. Since the last visit, has the subject been seen in the Emergency Room for their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____

III. Since the last visit, has the subject been admitted to the hospital due to their Crohn's Disease?

   YES:_____
   NO:_____
   If YES, how many times:_____
   If YES, please indicate the total number of days in the hospital:_____

Appendix N. Subject Medication Log

Instructions: As a participant in this study, it is also important to keep a record of all mediations you take (new and old) throughout the study. Please take this sheet home with you and write down any medications you take during the study. It will be VERY important that you bring this sheet back to your doctor's office and speak with your doctor about everything you have written down.

Name of Medication	Date you took first dose	Date you took last dose	What dose of medicine did you take?	How often did you take the medicine?	Why did you take the medicine?

Appendix O. Subject Dosing diary

Instructions: To be completed for every study dose. The areas shaded in grey are visits when the dose should be administered at the study doctor's office. The non-shaded areas should be completed for every dose administered at home. Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please refer to the Self Injection Instructions provided to you for additional dosing information. Call the doctor's office if you are having problems administering your study drug.

Study Entry - Week 4

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Study Entry					
	Week 2					
	Week 3					
	Week 4					

Week 5 - Week 8

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 5					
	Week 6					
	Week 7					
	Week 8					

Week 9 - Week 12

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 9					
	Week 10					
	Week 11					
	Week 12					

Week 13- Week 24

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 13					
	Week 14					
	Week 15					
	Week 16					
	Week 17					
	Week 18					
	Week 19					
	Week 20					
	Week 21					
	Week 22					
	Week 23					
	Week 24					

Week 25 - Week 36

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 25					
	Week 26					
	Week 27					
	Week 28					
	Week 29					
	Week 30					
	Week 31					
	Week 32					
	Week 33					
	Week 34					
	Week 35					
	Week 36					

Week 37 - Week 48

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 37					
	Week 38					
	Week 39					
	Week 40					
	Week 41					
	Week 42					
	Week 43					
	Week 44					
	Week 45					
	Week 46					
	Week 47					
	Week 48					

Week 49 - Week 60

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 49					
	Week 50					
	Week 51					
	Week 52					
	Week 53					
	Week 54					
	Week 55					
	Week 56					
	Week 57					
	Week 58					
	Week 59					
	Week 60					

Week 61 - Week 72

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
	Week 61					
	Week 62					
	Week 63					
	Week 64					
	Week 65					
	Week 66					
	Week 67					
	Week 68					
	Week 69					
	Week 70					
	Week 71					
	Week 72					

Week 73 - Week 84

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 73					
	Week 74					
	Week 75					
	Week 76					
	Week 77					
	Week 78					
	Week 79					
	Week 80					
	Week 81					
	Week 82					
	Week 83					
	Week 84					

Week 85 - Week 96

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 85					
	Week 86					
	Week 87					
	Week 88					
	Week 89					
	Week 90					
	Week 91					
	Week 92					
	Week 93					
	Week 94					
	Week 95					
	Week 96					

Week 97 - Week 104

Subject Initials: _____ Subject Study #: _____

Date day/mm/yr	Day or Week #	Time of Study Drug Administration	Dose (mL) Administered	Kit #	Initials of Person Administering Study Medication	Comments
18/MAR/04	EXAMPLE	9:35 am	0.8		MM	none
	Week 97					
	Week 98					
	Week 99					
	Week 100					
	Week 101					
	Week 102					
	Week 103*					

*The dose at Week 103 will only be taken if you are on weekly dosing.

Appendix P. Self Injection Instructions

Subject Instructions

0.8 mL or 0.4 mL dose

(Administered as a single dose-prefilled syringe (PFS))

Protocol M06-807

Tables of Contents

Study Drug Dosing Schedule **Open-Label (PFS)**

Subject Number:_____

You will require subcutaneous (SC) injections throughout the study.

Injections at scheduled study visits (Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96) will be done during your visit, at the doctor's office. On weeks between office visits, study drug will be self-administered at home by you or someone trained to give you the injections.

One pre-filled syringe will contain 0.8 mL of liquid. The total available dose is 0.8 mL. The drug should be administered in one (1) SC injection, on the same day of the week for each dose.

Please return all used and unused syringes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary.

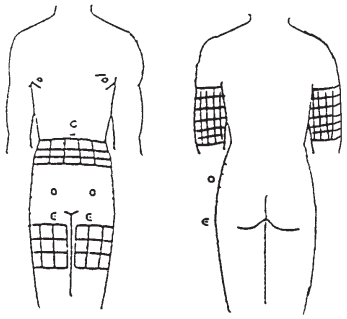
Remember to complete your dosing diary after each injection and to call the doctor's office if you are having problems administering your study drug.

General Information **PFS**

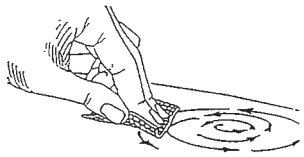
- Prefilled syringes will be labeled "adalimumab."
- Store all adalimumab prefilled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study coordinator.
- 0.8 mL = 0.8 cc
- Study drug should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study drugs. ***Prefilled syringes (used and unused) must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.
- Whenever possible, have someone with you for at least 15 to 30 minutes after your injection.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call 911**, or proceed to your nearest emergency room.

Injection Procedures **PFS**

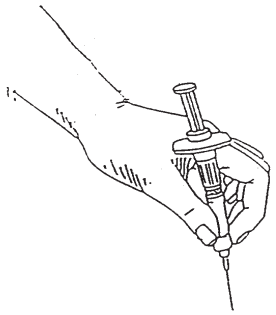
1. Clean your workspace, gather your supplies, and wash your hands.



2. Identify the area on your abdomen or thigh (or upper arm if not self injecting). Make sure the area you choose does not have any redness, tenderness, swelling, bruising, or psoriasis. The area must also be at least 2 cm (approximately 1 inch) away from the previous injection site. ***IT IS VERY IMPORTANT TO CHANGE THE INJECTION SITE EVERY TIME!!!***

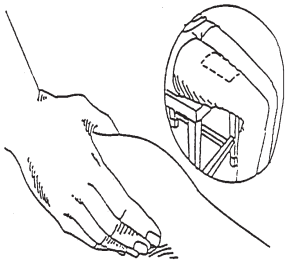


3. Using a circular motion (starting at the injection site and moving outward) clean the selected injection site with an alcohol pad. Allow skin to dry.
4. Remove the needle cap. Do not touch the needle. Expel any air bubbles from the syringe by tapping on the syringe. If the needle becomes contaminated, discard all supplies and obtain a new syringe of study drug.
5. Once the air is expelled from the syringe, the amount of solution in the syringe should be 0.8 mL.

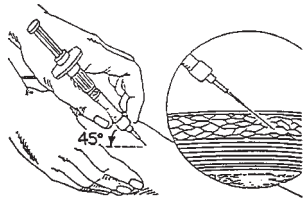


6. Hold the syringe "like a dart" between your thumb and first finger close to the syringe/needle connection.

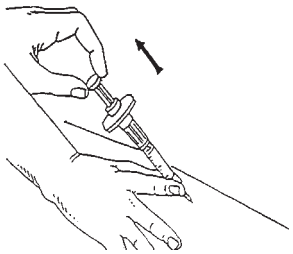
PFS



7. With your other hand, pinch the skin around the injection site, forming a bulge in the skin.

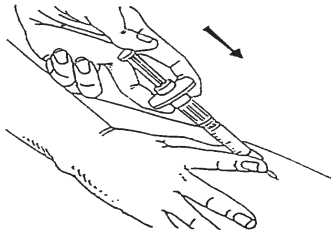


8. Insert the needle into the skin at a 45-degree angle. Release pinched skin.



9. GENTLY pull back on the syringe plunger. If blood appears, withdraw needle - DO NOT INJECT! Contact your study center immediately for further instructions.

10. Inject drug by pushing slowly on syringe plunger with thumb.



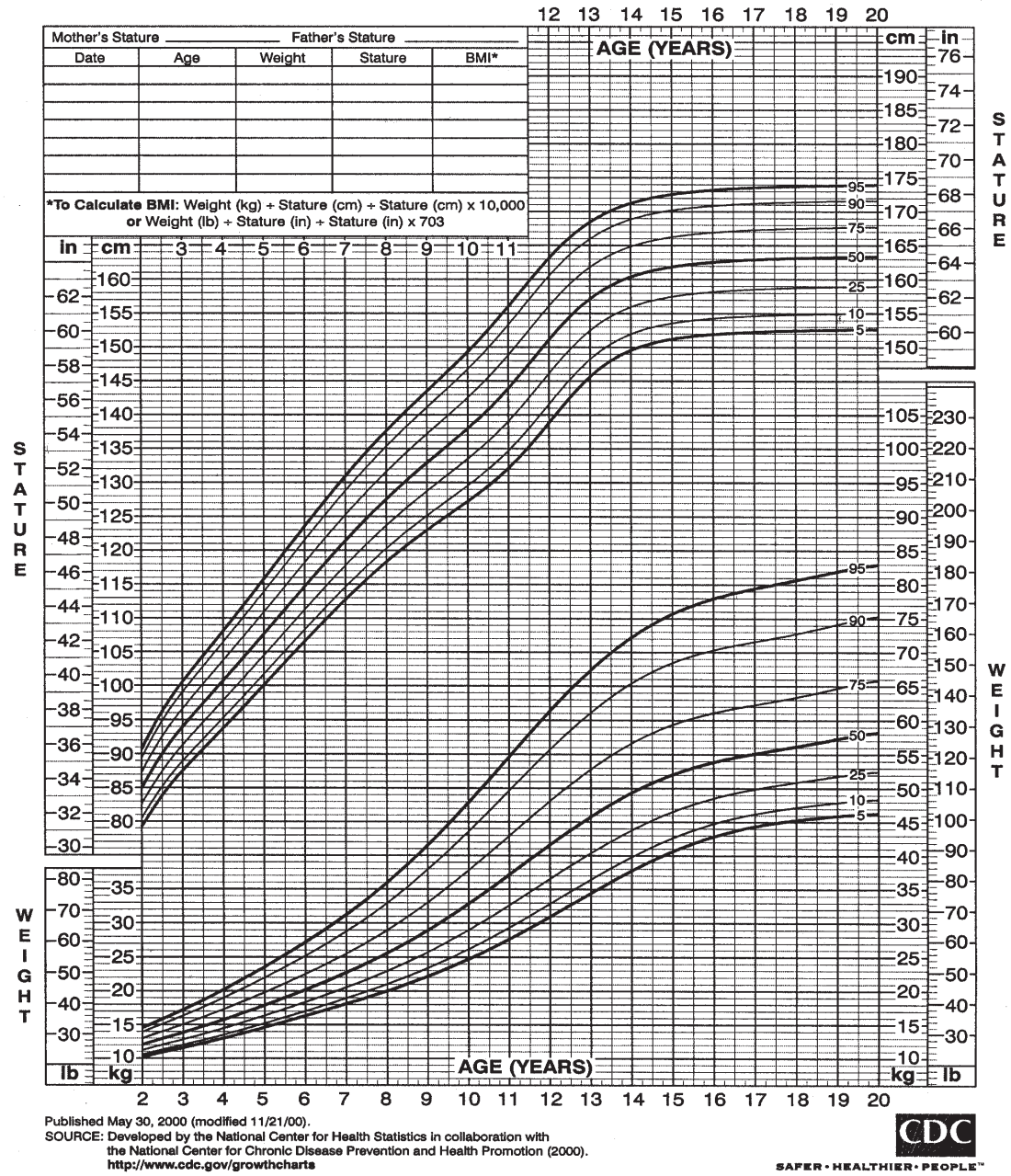
11. Remove needle while maintaining a 45-degree angle.

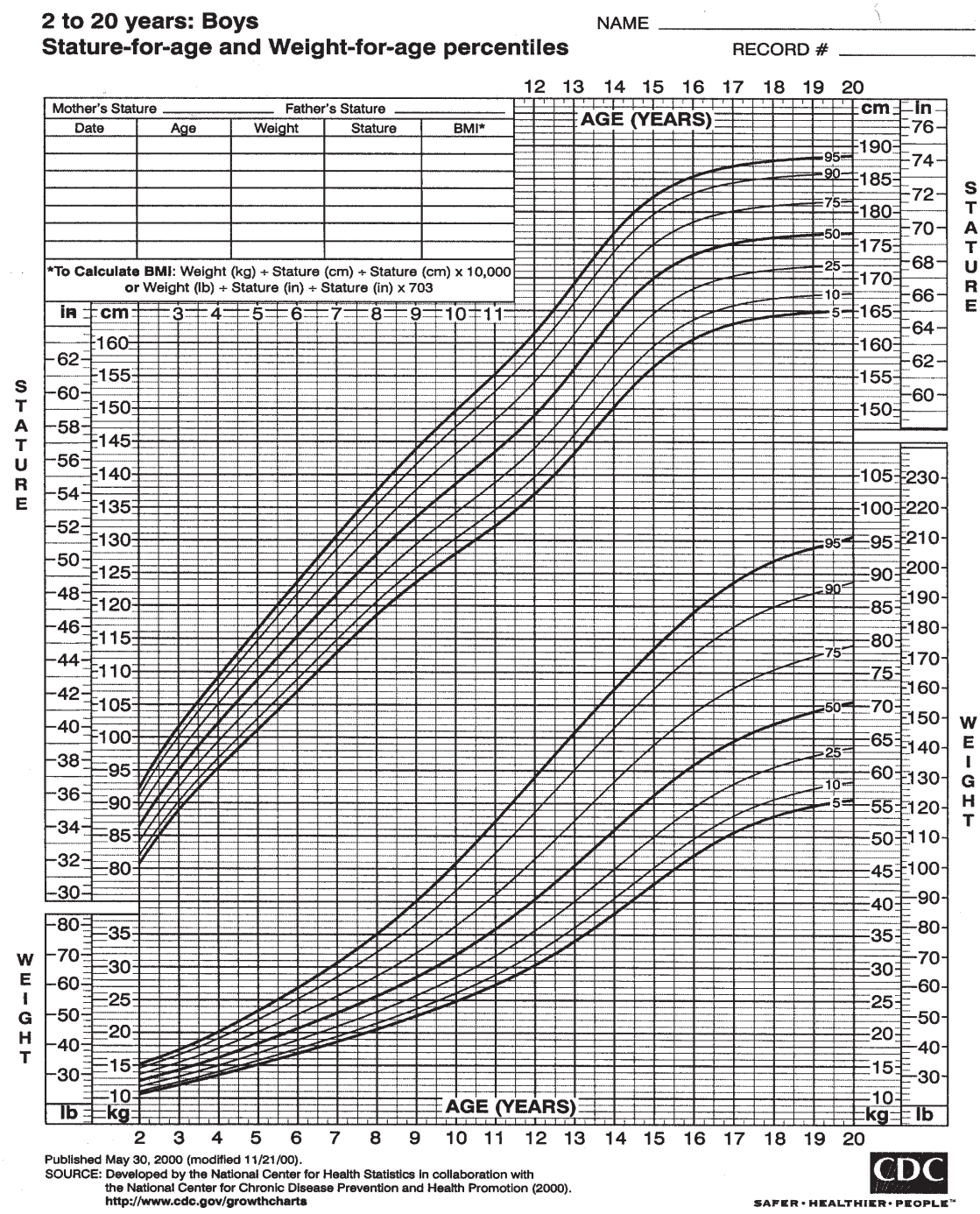
12. You may apply a Band-Aid over the injection site and apply gentle pressure, if necessary. DO NOT RUB SITE.

13. ***DO NOT*** RECAP NEEDLE. ***DO NOT*** SEPARATE THE NEEDLE FROM THE SYRINGE BEFORE DISPOSING. Discard used syringes into Sharps Container.

EACH TIME THAT YOU GIVE YOURSELF AN INJECTION OF STUDY DRUG, REMEMBER TO RECORD THE INFORMATION ON YOUR SUBJECT DOSING DIARY.

Appendix Q. Standard Weights




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
SAFER · HEALTHIER · PEOPLE™

Appendix R. Abbott Laboratories Site Drug Accountability Form

Investigator Name:_____ **Drug Name: Adalimumab**

Site Number:_____ **Unit: Vial**

Date Received	Lot Number	Kit Number	Number of Units/Kits	Dispensed by (Initials) & Date Dispensed	Subject Number	Number of Used Vials Disposed	Number of Unused Vials Returned to Abbott	Site Staff Initials	Date	Monitor Initials	Date

Appendix S. Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD) - Caregiver

The following questions ask about the effect of your child's Crohn's disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

   The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your child's Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your child's Crohn's disease. Do not include time you missed for your child to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your child's Crohn's disease affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your child's Crohn's disease *affected your work only a little, choose a low number. Choose a high number if your child's* Crohn's disease *affected your work a great deal.*

Consider only how much your child's Crohn's disease affected your productivity while you were working.

My child's Crohn's disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My child's Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your child's Crohn's Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your child's Crohn's Disease affected your activities only a little, choose a low number. Choose a high number if your child's Crohn's Disease affected your activities a great deal.

Consider only how much your child's Crohn's disease affected your ability to do your regular daily activities, other than work at a job.

My child's Crohn's disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My child's Crohn's disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:CD-Caregiver (US English)

Document Approval

Study M06-807 - 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 - EudraCT 2007-006494-90 - 11Jan08

Version: 1.0 **Date:** 11-Jan-2008 10:13:15 PM **Abbott ID:** 01112008-00AB618C879AE5-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	11-Jan-2008 08:14:02 PM	Approver
	11-Jan-2008 09:08:50 PM	Approver
	11-Jan-2008 09:24:32 PM	Approver
	11-Jan-2008 10:13:08 PM	Approver