

1.0 Title Page

CLINICAL STUDY PROTOCOL M11-290

A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis

Incorporating Amendment 1, Administrative Change 1, Amendment 2, Administrative Change 2, Amendments 3, 4 and 5

AbbVie Investigational
Product: Adalimumab
Date: 20 November 2018
Development Phase: 3
Study Design: This is a Phase 3, multicenter, randomized, double-blind study designed to evaluate the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in pediatric subjects with moderate-to-severe ulcerative colitis (UC).

EudraCT Number: 2013-003032-77
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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.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	27 June 2013
Amendment 1	06 September 2013
Administrative Change 1	20 November 2013
Amendment 2	02 April 2014
Administrative Change 2	16 May 2014
Administrative Change 3	22 May 2015
Amendment 3	28 August 2015
Amendment 4	02 November 2017

The purpose of this amendment is to:

- Modify statistical analyses and ranking of study endpoints.
***Rationale:** To update external placebo rates as derived from meta-analyses. To specify confirmatory testing of combined adalimumab dose groups as well as individual adalimumab dose groups versus external placebo with multiplicity adjustment for co-primary and ranked secondary endpoints (number reduced to four based on availability of external placebo data) . Other secondary analyses will be exploratory.*
- Reflect final sample size of 93 subjects (and up to approximately 9 subjects in the Japan sub-study).
***Rationale:** To ensure the needed sample size for planned testing of combined adalimumab dose groups as well as individual adalimumab dose groups versus external placebo.*
- Adapted the number of samples collected for adalimumab, AAA, Infliximab, HACA assays based on final sample size.
- Incorporate minor typographical and grammatical changes and provide clarifications throughout the protocol.

An itemized list of all changes made to this protocol amendment can be found in [Appendix O](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M11-290
Name of Study Drug: Adalimumab	Phase of Development: 3
Name of Active Ingredient: Adalimumab	Date of Protocol Synopsis: 20 November 2018
Protocol Title: A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis	
Objective: The objective of the study is to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously (SC) in pediatric subjects with moderate to severe ulcerative colitis (UC).	
Investigators: Multicenter	
Study Sites: Approximately 50 sites worldwide for the main study and approximately 10 sites for the Japan sub-study.	
Study Population: Subjects with moderate-to-severe UC from the ages of 4 to 17 prior to Baseline dosing.	
Number of Subjects to be Enrolled: 93 subjects for the main study and up to approximately 9 subjects for the Japan sub-study	
Methodology: This is a Phase 3, multicenter, randomized, double-blind trial designed to evaluate the efficacy and safety of adalimumab in pediatric subjects with moderate to severe ulcerative colitis, who have failed therapy with corticosteroids and/or immunosuppressants.	

Methodology (Continued):

93 pediatric subjects for the main study (and up to approximately 9 subjects for the Japan sub-study) with moderate-to-severe UC (Mayo Score of 6 to 12 points with an endoscopy subscore of 2 to 3, confirmed by central reader) will be enrolled at approximately 50 sites worldwide (and approximately 10 sites for the Japan sub-study). The study will allow enrollment of up to 25% of anti-TNF experienced subjects. Prior to Amendment 4, subjects who met all of the inclusion criteria and none of the exclusion criteria were to be enrolled and randomized 3:2 at Baseline to one of two double-blinded adalimumab induction doses (high dose or standard dose). The randomization was to be stratified by baseline disease severity (per Mayo Score), prior exposure to anti-TNF, and corticosteroid use at Baseline. During the randomized double-blind induction period, subjects assigned to high induction dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects received adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Subjects randomized to the standard induction dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, adalimumab 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. After Amendment 4, subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and receive open-label adalimumab high induction dose. During the open-label induction period, subjects will receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects will receive adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the induction period until Week 8.

Prior to Amendment 4, at Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) were randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) and Induction dose in a 2:2:1 ratio to one of two adalimumab maintenance treatment groups (Standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or High dose [0.6 mg/kg (maximum dose of 40 mg) every week]) or to placebo, respectively.

After Amendment 4, at Week 8, subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) will be randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) in a 1:1 ratio to one of two adalimumab maintenance treatment groups (Standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or High dose [0.6 mg/kg (maximum dose of 40 mg) every week]).

Subjects will receive blinded treatment every week (ew) beginning at Week 8 and will remain on double-blinded therapy through Week 52.

- Subjects who are randomized to standard dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) every other week (eow) and will receive the matching placebo at the alternate week.
- Subjects who are randomized to high dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) ew.
- Subjects who were randomized to placebo prior to Amendment 4 receive matching placebo ew.

Methodology (Continued):

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the maintenance period until Week 52 and re-randomization to treatment for disease flare will be done according to Amendment 3 stipulations in these subjects.

At Week 8, subjects who have not achieved a clinical response per PMS will be discontinued. A safety evaluation call will be made 70 days after the last dose of study drug is administered to obtain follow-up information on any ongoing or new adverse events.

The duration of the study could be up to 66 weeks, which includes a Screening Period of up to 28 days, 8-week induction period and a 44-week double-blind maintenance period and a 70-day follow-up. Upon completion of the study, subjects will have the option to enroll into an open-label extension study where they will receive open-label adalimumab.

Treatment of Subjects with Disease Flare During the Study:

Criteria for Disease Flare are as follows:

- Subjects with a Week 8 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Week 8 score.

Subjects will be expected to remain on blinded therapy throughout the 44-week maintenance period.

However, subjects with a disease flare, may be re-randomized to receive the following blinded-treatment at or after Week 12:

- Subjects who are randomized to Standard maintenance dose (0.6 mg/kg [maximum dose of 40 mg] eow) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume receiving the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
- Subjects who are randomized to High maintenance dose (0.6 mg/kg [maximum dose of 40 mg] ew) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew).
- Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.

If a subject continues to meet the definition of disease flare (2nd time) following at least a 4-week course of blinded therapy since the subject has been re-randomized for disease flare, they may be switched to open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg]. *If a subject was re-randomized at Week 12 (to receive either re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]), then the earliest that subject could be evaluated to determine if the subject meets the criteria for disease flare for switch to OL (0.6 mg/kg [maximum of 40 mg]) weekly dosing is at Week 16.*

Methodology (Continued):

Treatment of Subjects with Disease Flare During the Study (Continued):

If a subject continues to meet the definition of disease flare (3rd time) following a 4-week course of open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab open-label 40 mg ew (maximum dose, not weight-based).

Subjects with persistent disease flare while on adalimumab 40 mg ew (max dose) may be withdrawn from the study at the investigator's discretion.

During open-label rescue therapy, subjects who are responders and have been in remission for at least 8 consecutive weeks ($PMS \leq 2$ with no individual subscore > 1) may have their dosage decreased from ew to eow. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose de-escalation.

If subjects demonstrate disease flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to adalimumab ew dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose re-escalation.

For subjects who meet the criteria for dose change, blood samples (adalimumab, AAA and hs-CRP) will be collected just prior to receiving any dose change (blinded therapy, escape to open-label adalimumab, dose de-escalation and dose re-escalation).

Subjects are allowed to be treated with stable doses of UC-related concomitant medications during the study, with the following exceptions and requirements:

- At or after Week 4, subjects taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered based on the investigator's discretion. A proposed tapering schedule is specified in Section 5.3.1.1.
- From Week 4 to Week 12, if the subject should experience an increase in symptoms after corticosteroid was tapered, the subject may have their corticosteroid dose increased back up to the corticosteroid dose at Baseline. This increase must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Subjects who experience disease flare at or after Week 12 are allowed to change their dose or initiate treatment with corticosteroids, immunosuppressant or 5-ASA; these increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.
- Immunosuppressant therapy may be discontinued at or after Week 12 at the investigator's discretion.

At each study visit, in addition to routine physical examination including evaluation of extra intestinal manifestations and calculation of the PMS and PUCAI, the following will be collected:

- Anthropometric evaluations at Baseline, Week 26 and Week 52/Premature Discontinuation for determination of body mass index (BMI), and "z" scores for height and weight.
- IMPACT III Quality of Life questionnaire at Baseline, Week 8, Week 26 and Week 52/Premature Discontinuation Visit will be completed for subjects 9 years or older at the Baseline study visit.
- Bone age determination by x-ray of the wrist at Screening and at Week 52/Premature Discontinuation Visit in subjects who have not completed linear growth.
- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26 Week 34 and Week 52/Premature Discontinuation Visit and at Unscheduled Visit requiring dose change.

Methodology (Continued):

Treatment of Subjects with Disease Flare During the Study (Continued):

- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 8, Week 26 and Week 52/Premature Discontinuation Visit and at Unscheduled Visit requiring dose change.
- Tanner stage at Baseline, Week 26 and Week 52/Premature Discontinuation Visit.
- Endoscopy subscore at Screening and Week 52/Premature Discontinuation Visit.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subjects from the ages of 4 to 17 prior to baseline dosing.
2. Subjects with a diagnosis of UC for at least 12 weeks prior to screening confirmed by endoscopy with biopsy.

A colonoscopy will be performed during the screening period unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis without evidence of dysplasia, colon cancer or infection). In this case the screening endoscopy may be either a colonoscopy or a flexible sigmoidoscopy.

If the subject underwent an endoscopy within 56 days of Baseline, and a video recording of the endoscopy is available, the video recording may be used and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met and all technical requirements are fulfilled.

Note:

- If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must also be performed.
 - Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.
3. Active ulcerative colitis with a Mayo Score of 6 – 12 points and endoscopy subscore of 2 – 3 (confirmed by central reader) despite concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):
 - Oral prednisone of ≥ 2 mg/day or equivalent, but not exceeding 40 mg/day, or oral budesonide ≥ 3 mg/day, but not exceeding 9 mg/day, with a stable dose for at least 7 days prior to Baseline; and/or
 - At least a consecutive 28-day course of azathioprine or 6-MP or methotrexate (MTX) prior to Baseline, with a stable dose prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of 230 – 450 pmol/ 8×10^8 RBC on the current dosing regimen or MTX ≥ 15 mg/m² body surface area/week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Note: If subjects are on both oral corticosteroid and immunosuppressants BOTH of the drugs need to meet the above criteria; and/or

- Concurrent therapy with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) is not required for subjects who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

4. Parent or guardian has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed or before any concomitant medication is discontinued for the purpose of this study. Pediatric subjects will be included in all discussions in order to obtain verbal and/or written assent.
5. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
6. Subject has a negative TB Screening Assessment.
If a subject has a positive (≥ 5 mm induration) PPD test and/or IGRA test at Screening, a CXR (PA and lateral view) must be performed for evaluation of active TB disease. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.
7. If female, subject who is either not of childbearing potential, defined as pre-menstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.
Examples of approved methods of birth control include the following (see local informed consent for more detail):
 - Total abstinence from sexual intercourse;
 - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
 - Hormonal contraceptives for 90 days prior to study drug administration;
 - A vasectomized partner.
8. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

Main Exclusion:

1. Subject with Crohn's disease (CD) or indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subjects with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Therapeutic enema or suppository within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of colectomy or subtotal colectomy (with ostomy) or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil, within 30 days prior to Baseline.
7. Female subjects who are breast-feeding or considering becoming pregnant during the study.
8. Positive pregnancy test at Screening or Baseline.
9. History of clinically significant drug or alcohol abuse in the last 12 months.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

10. Subjects on azathioprine or 6-mercaptopurine (6-MP) or MTX and subjects:
 - Have not been on stable doses of these medications for at least 28 days prior to Baseline; or
 - Have discontinued these medications within 28 days of Baseline.
11. Subjects on oral aminosalicylates who:
 - Have not been on stable doses of these medications for at least 14 days prior to Baseline; or
 - Have discontinued use of aminosalicylates within 14 days of Baseline.
12. Subjects on growth hormone who have not been on a stable dose for at least 4 weeks prior to Baseline.
13. Subjects on oral corticosteroids who:
 - Have not been on stable doses of these drugs for at least 7 days prior to Baseline; or
 - Discontinued use of oral corticosteroid within 14 days of Baseline; or
 - Have been taking both budesonide and prednisone (or equivalent) simultaneously.
14. Received intravenous corticosteroids within 5 days prior to Screening or during the Screening Period.
15. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.
16. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.
17. Previous treatment with adalimumab or previous participation in an adalimumab clinical study.
18. Positive *Clostridium difficile* (*C. difficile*) stool assay during the Screening Period.
19. Currently receiving total parenteral nutrition (TPN).
20. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
21. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).
22. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
23. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
24. Subject with a positive result for the Hepatitis B surface antigen (HBs Ag) or any HBV DNA PCR result that meets or exceeds detection sensitivity will be excluded.
25. Chronic recurring infections or active TB.
26. Subject has been treated with any investigational drug of chemical or biologic nature or any investigational procedure (including previous fecal transplantation) within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline Visit.
27. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
28. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab (Tysabri[®]) or efalizumab (Raptiva[®]) or rituximab (Rituxan[®]).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

29. Known hypersensitivity to adalimumab or its excipients.
30. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

If the Screening endoscopy shows evidence of dysplasia or malignancy, subject may not be enrolled in the study.

31. Screening laboratory and other analyses show any of the following abnormal results:
 - ECG – with clinically significant abnormalities;
 - Aspartate transaminases (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range;
 - Total bilirubin ≥ 3 mg/dL;
 - Serum creatinine > 1.6 mg/dL;
 - Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Product:	Adalimumab
Induction Dose:	<p>Body weight adjusted induction dose regimen</p> <p>Prior to Amendment 4 subjects were randomized to receive one of 2 double-blind adalimumab induction doses.</p> <p><u>Standard Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and matching placebo at Week 1. Subjects received 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects received a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p> <p><u>High Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and Week 1. Subjects received 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects received a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p> <p>After Amendment 4 subjects will receive the open-label adalimumab high induction dose.</p> <p><u>High Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and Week 1. Subjects will receive 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects will receive a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p>

Double-Blind Maintenance Doses (in Week 8 PMS Responders only):	<p>Body weight adjusted maintenance dose regimen</p> <p><u>Blinded adalimumab Standard dosing regimen:</u> 0.6 mg/kg (maximum dose of 40 mg) eow with matching placebo at the alternate week</p> <p><u>Blinded adalimumab High dosing regimen:</u> 0.6 mg/kg (maximum dose of 40 mg) ew</p> <p>Subjects who were randomized to placebo (prior to Amendment 4) receive placebo ew.</p> <p>At or after Week 12 subjects who demonstrate a disease flare may be re-randomized to receive the following blinded-treatment.</p> <ul style="list-style-type: none"> • Subjects, who are randomized to standard maintenance dose, will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume to receiving the standard dose adalimumab (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule. • Subjects who are randomized to high maintenance dose, will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume to receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew). • Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
Open-Label Maintenance Doses:	<p>High dose body weight adjusted.</p> <p>0.6 mg/kg (maximum dose of 40 mg) ew</p> <p>If a subject continues to meet the definition of disease flare following a 4-week course of open-label adalimumab ew at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab 40 mg ew (maximum dose, not weight-based).</p>
Mode of Administration:	<p>Subcutaneous injection (SC)</p>
Reference Therapy:	<p>NA (after Amendment 4); Placebo (prior to Amendment 4)</p>
Dose:	<p>NA</p>
Mode of Administration:	<p>NA (after Amendment 4); Subcutaneous injection (SC) (prior to Amendment 4)</p>

Duration of Treatment: 52 weeks

- The subjects will visit the site at Screening, Baseline, Weeks 1, 2, 4, 8, 12, 18, 26, 34, 42, and 52/Premature Discontinuation and Unscheduled Visits.
- Subjects who qualify will be given the opportunity to enroll into an open-label study of the Long-term Safety and Tolerability of Repeated Administration of Adalimumab.

A 70-Day Follow-Up phone call will be completed for all subjects who either terminate early from the study or do not rollover into the extension study.

Criteria for Evaluation:

Efficacy analysis will be based on the Intent-To-Treat-Efficacy (ITT-E) population for the induction period and modified ITT (mITT) population for the maintenance period. The ITT-E population is a subpopulation of the ITT population, which consists of all subjects who received at least one SC injection of the study medication during the induction period. Subjects who receive open-label high induction dose, because they enrolled after Protocol Amendment 4 was released, will be excluded from the ITT-E population. The mITT population consists of all Week 8 PMS Responders among the ITT population who were randomized at Week 8 and received at least one SC injection of the study medication during maintenance period.

The safety analysis set will include all subjects who received at least one SC injection of the study medication.

Efficacy:

This study will utilize the Mayo Score, PMS and Mayo subscores to measure efficacy. The PUCAI will also be utilized as applicable. Please refer to 'Statistical Methods' for details on the sequentially rejective multiple test procedure of the dose groups used in this study versus external placebo for co-primary and ranked secondary endpoints.

Efficacy Endpoints

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1);
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo Score (defined as a Mayo Score ≤ 2 and no individual subscore > 1).

Ranked secondary efficacy endpoints are:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;
4. Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional exploratory secondary analyses:

- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 8;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI \geq 20 points from Baseline) at Week 8;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI \geq 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;
- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;
- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects in PMS response over time;
- Proportion of subjects in PMS remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points;
- Change from Baseline in hemoglobin, hematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with extraintestinal manifestations (EIM) at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy subscore of 0 or 1 (without friability) at Week 52;
- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without RBS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Change from Baseline in Mayo Score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy subscore at Week 52;
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

Pharmacokinetic:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline, Weeks 2, 4, 8, 12, 26, 34 and 52/Premature Discontinuation Visits, and at Unscheduled Visits requiring dose change. Blood samples will be collected for the measurement of serum anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Weeks 4, 8, 26 and 52/Premature Discontinuation Visits and at Unscheduled Visits requiring dose change. Blood samples will be collected for the measurement of serum Infliximab and HACA at Baseline (prior to dosing).

Safety:

Adverse events, laboratory data, and vital signs will be assessed at all visits throughout the study.

Statistical Methods:

Efficacy:

The efficacy analysis will be performed in the ITT-E set for the induction period and in the mITT set for the maintenance period. NRI method will be used to impute missing values for binary efficacy endpoints. Subjects who do not complete the induction period or who receive rescue therapy during the maintenance period will be considered as failures from that time point forward. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

The confirmatory efficacy analyses for the co-primary endpoints and ranked secondary endpoints are based on the following external placebo assumptions.

Statistical Methods (Continued):

External Placebo Assumptions for Co-Primary and Ranked Secondary Efficacy Endpoints

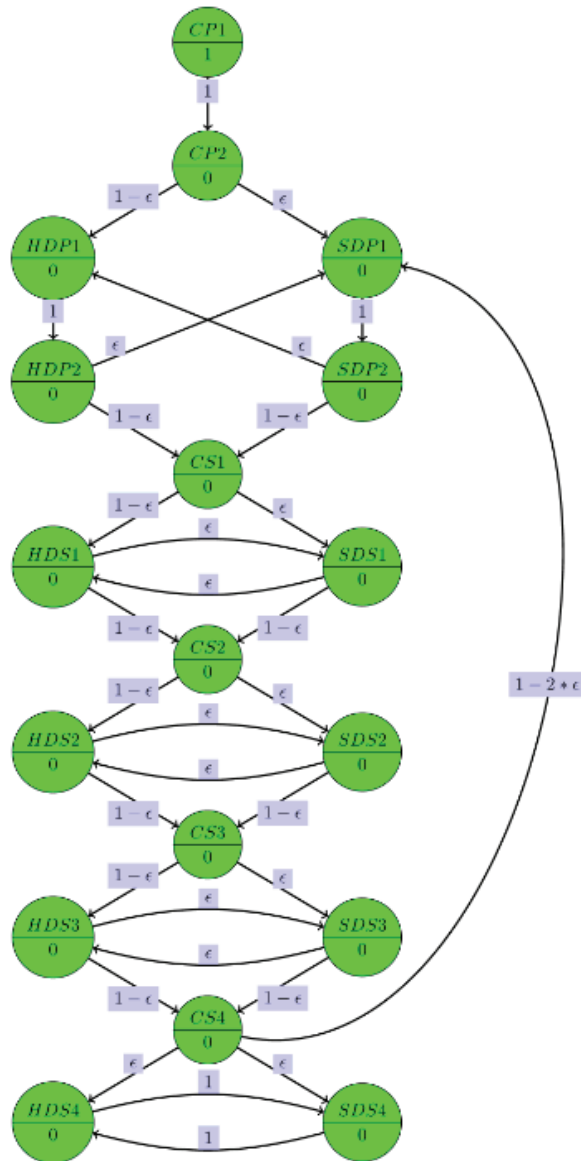
Endpoint	External Placebo Rate (95% CI Upper Limit from Meta-Analysis)
Week 8 PMS Remission	19.83%
Week 52 FMS Remission in Week 8 Responders per PMS	18.37%
Week 52 FMS Response in Week 8 Responders per PMS	26.10%
Week 52 Mucosal Healing in Week 8 Responders per PMS	22.03%
Week 52 FMS Remission in Week 8 Remitters per PMS	14.79%
Week 52 FMS Remission in Week 8 Responders per PMS with CS at Baseline and Discontinued CS prior to Week 52	24.08%

FMS = Full Mayo Score; PMS = Partial Mayo Score; CS = Corticosteroids

Co-primary and ranked secondary endpoints will be summarized by treatment group with 95% confidence intervals (CI) and adalimumab dose groups will be tested against external placebo in a sequentially rejective multiple test procedure in order to ensure that the multiple significance level of 5% is controlled, using one sample two-sided Chi-square tests. The below graph describes the structure of the multiple test procedure that starts with testing the co-primary endpoints for the combined high and standard adalimumab dose groups versus external placebo and then individual dose groups versus external placebo separately:

Statistical Methods (Continued):

Multiple Test Procedure for the Co-Primary and Ranked Secondary Endpoints



Assuming $\epsilon = 0.0005$; C = testing the endpoint for the combined high and standard adalimumab dose groups against external placebo; HD = testing the endpoint for the high adalimumab dose against external placebo; SD = testing the endpoint for the standard adalimumab dose against external placebo; P_1 = co-primary induction endpoint; P_2 = co-primary maintenance endpoint; S_i = ranked secondary endpoint i ($i=1, \dots, 4$)

Statistical Methods (Continued):

Additional exploratory secondary endpoints that are of the categorical type will be summarized by treatment group with 95% CIs. Additional exploratory secondary endpoints that are of the continuous type will be analyzed as changes from baseline, and reported by treatment group including 95% CIs.

The following subset of endpoints will be tested for the high adalimumab dose against the standard adalimumab dose in an exploratory manner:

- Proportion of subjects in PMS clinical remission at Week 8;
- Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission at Week 8;
- Proportion of subjects in PUCAI response at Week 8.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics. In addition, pharmacokinetic model based analyses will be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

AAA will be evaluated for each subject and each regimen, and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated. HACA will be evaluated for each subject and each regimen, and rates of HACA positive will be calculated.

Safety:

Treatment-emergent Adverse Events (AEs) and serious adverse events (SAEs) will be summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. A summary of AEs by severity and relationship to study drug will be performed. Changes in laboratory and vital sign data will be summarized using descriptive statistics. Shift tables will be provided.

Statistical Methods (Continued):

Sample Size:

The co-primary endpoints will be tested first for the combined high and standard adalimumab dose groups versus external placebo and then for the individual dose groups versus external placebo separately, controlling the multiple significance level of 5%. For each individual test the nominal power is calculated.

Assuming a 48% remission rate per PMS at Week 8 for the combined standard and high adalimumab induction dose groups and a remission rate per PMS of 19.83% for external placebo, a total of 77 subjects (high:standard = 46:31) in ITT-E population provides at least 99% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming a 36% remission rate per Mayo Score at Week 52 for the combined standard and high maintenance dose groups and a remission rate per Mayo Score of 18.37% for external placebo, a total of 57 subjects in the combined adalimumab maintenance dose groups in mITT population (e.g., high:standard = 28:29) provide 88% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming that the high adalimumab dose regimen is associated with higher efficacy than the standard adalimumab dose regimen, assuming a 52% remission rate per PMS at Week 8 for the high adalimumab induction dose group and a remission rate per PMS of 19.83% for external placebo, 46 subjects in the high adalimumab induction dose group of ITT-E population provide at least 99% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Assuming a 41% remission rate per Mayo Score at Week 52 for the high adalimumab maintenance dose group and a remission rate per Mayo Score of 18.37% for external placebo, a total of 28 subjects in the high adalimumab maintenance dose group of mITT population provide at least 80% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Based on the assumption of a 75% response rate at Week 8, 93 subjects will have to be included in the study (including ~12 internal placebo subjects in the maintenance part of the study who were included prior to Amendment 4) to ensure 57 subjects in the combined adalimumab maintenance dose groups.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AAA	Anti-adalimumab antibody
ADA	Adalimumab
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
BLA	Biologics License Application
BUN	Blood urea nitrogen
CD	Crohn's disease
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CRP	C-Reactive protein
CTC	Common Toxicity Criteria
CXR	Chest x-ray
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
EC	Ethics Committee
ECG	Electrocardiogram
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EIM	Extraintestinal manifestation
eow	every other week
ew	every week
EP	European Pharmacopoeia
ESR	Erythrocyte sedimentation rate

FC	Fecal calprotectin
FDA	Food and Drug Administration
FMS	Full Mayo Score
GCP	Good Clinical Practice
HACA	Human antichimeric antibody
HAQ	Health Assessment Questionnaire
HAV-IgM	Hepatitis A virus immunoglobulin M
HbsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
hs-CRP	High Sensitivity C-Reactive protein
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MTX	Methotrexate
NDC	National Drug Code
n_{miss}	Number of non-missing observations
OL	Open-label
PA	Posteroanterior
PBO	Placebo
PD	Premature Discontinuation
PG	Pharmacogenetic
PIP	Pediatric Investigational Plan

PK	Pharmacokinetics
PMS	Partial Mayo Score
POR	Proof of Receipt
PPD	Purified protein derivative
PUCAI	Pediatric Ulcerative Colitis Activity Index
QTc	QT interval corrected for heart rate
RA	Rheumatoid arthritis
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
sc	Subcutaneous
TB	Tuberculosis
Th1	Type 1 T helper
TNF	Tumor necrosis factor
TPN	Total parenteral nutrition
UC	Ulcerative Colitis
USP	United States Pharmacopoeia
WBC	White blood cell

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3.0 Introduction

3.1 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF- α but not to lymphotoxin- α (TNF- β).

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 also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in US and EU for the treatment of RA in 2002 and 2003, respectively. Additional indications have been approved in the US and EU including Ps, PsA, AS, CD, JIA and UC. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

3.2 Ulcerative Colitis and Current Treatments Overview

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). It is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and

remission. The general clinical features of UC are similar in adults and children; however, there are differences in the presentation and progression of the disease. While in adults, the vast majority have limited or left-sided colitis in children proximal extension of disease¹ and pancolitis involving the entire colon is more common,² and extra-intestinal manifestations seem to be more frequent. UC onset can occur at any age, but it is extremely rare in infants, infrequent in early childhood, and is more commonly diagnosed in late adolescence and early adulthood. Less than 1% of pediatric IBD cases occur during the first year of life, most of which are eventually diagnosed as CD and not UC.³ Studies frequently report no,^{4,5} or very few cases of UC below age 5 (11 of 211 pediatric UC cases in Great Britain and Ireland⁶). Reported incidence of UC in Europe before age 10 is also very low (per 100,000; Northern France 0.3 for ages 5 to 10,⁷ Scotland 1.4 for ages 7 to 11,⁸ and Northern Stockholm 1.1 for ages 5 to 9⁹). In Northern France, crude incidence of UC per 100,000 was 0.1, 0.3, 1.1, and 2.5 for age groups 0 to 5, 5 to 10, 10 to 15, and 15 to 17, respectively.⁷ A prospective, population-based study in Poland in children less than age 18 reported an increase after age 10 in UC incidence (per 100,000 patient years, 0.1 age 0 to 2; 0.7 age 3 to 5; 0.9 age 6 to 10; 1.9 age 11 to 18).¹⁰ In most pediatric studies, the median age of symptom onset was 12 years.²

The burden of UC on the healthcare system is profound, accounting for nearly 470,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone.¹¹

The diagnostic measures to confirm the presence of UC are essentially the same in adults and children. The diagnosis of UC is suspected on clinical grounds and supported by diagnostic testing, and elimination of infectious causes, although infection can be present in patients with UC.² Bloody diarrhea accompanied by tenesmus is the leading symptom in 84% to 94% of children.¹ After exclusion of infections and other causes, UC should be suspected in children if bloody diarrhea is chronic (≥ 4 weeks) or recurrent (≥ 2 episodes within 6 months), particularly when growth failure and/or pubertal delay, family history of UC/IBD, increased inflammatory markers, or anemia are present.² It should be noted that growth failure is half as common in UC than in CD, perhaps because the interval

between symptoms and diagnosis is generally shorter.² The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published the Porto Criteria for the diagnosis of IBD (UC, CD, and IC) in children in 2005.

Disease of moderate or severe activity may often be associated with anorexia, nausea, weight loss, and fever, as well as symptoms associated with anemia and hypoalbuminemia. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extraintestinal complications include arthritis (sacroiliitis and ankylosing spondylitis), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.¹²

The pharmacological treatment of UC in childhood is largely the same as in adulthood. Conventional pharmaceutical therapies do not completely abate the inflammatory process and have significant side effects. Conventional therapies for the induction of remission have included anti-inflammatory agents (5-aminosalicylic acid [5-ASA] derivatives and corticosteroids) and the immunomodulatory agent cyclosporine. 5-ASA derivatives as well as immunomodulatory agents (azathioprine or 6-mercaptopurine [6-MP]) have been used for the maintenance of remission.¹³ Corticosteroids are not effective for the maintenance of remission. In addition to the induction and maintenance of clinical remission, absence of adverse effects on linear growth and maturation is demanded from therapy of pediatric UC. Similar to adults, corticosteroid dependence is frequent, but long-term corticosteroids are absolutely contraindicated because they do not maintain remission and have a negative effect on linear growth and bone mineralization.² Infliximab (a chimeric monoclonal anti-tumor necrosis factor [TNF]- α antibody) was approved in Europe for the treatment of pediatric patients with severe UC and in the US for the treatment of pediatric patients with moderate to severe UC based on the results of a recent study.¹⁴

The safety and efficacy of adalimumab for the induction and maintenance of clinical remission in adult subjects with moderately to severely active UC has been studied in two completed double-blind clinical trials (Study M06-826 and Study M06-827) and a completed open-label study (Study M10-223).¹⁵⁻¹⁸ In addition, adalimumab has shown clinically relevant improvements in IBDQ scores compared to placebo for up to 52 weeks in these subjects.¹⁹

3.3 Safety Information

Adalimumab therapy has a well established and well described safety profile in adults based on extensive postmarketing experience and continued clinical trial-subject exposure since the first approved indication in 2002 for rheumatoid arthritis. In general, the safety profile observed in pediatric studies is consistent with that in the adult population. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF inhibitor class-wide exploration of the rare appearance of malignancy in subjects who are 30 years old or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event Reporting.

3.3.1 Differences Statement

Pediatric subjects with moderate-to-severe UC between the ages of 4 and 17 who have failed conventional therapy with corticosteroids or immunosuppressants will be considered for participation in the study. To date, the efficacy, safety and the pharmacokinetics of adalimumab in pediatric subjects with moderate-to-severe ulcerative colitis (UC) have not been evaluated in a double-blind, controlled trial.

3.4 Benefits and Risks

Extensive clinical and postmarketing experience exists with adalimumab in a wide range of disease states including the IBD indications Crohn's disease and UC. The safety profile of adalimumab in those indications is well established with more than 50,000 patient-years of adalimumab clinical trial experience. The clinical studies in adult UC have not altered this safety profile and demonstrated a positive benefit/risk balance. Conditions which may present a risk specifically for subjects with UC are exclusion criteria in this study (e.g., evidence of colonic dysplasia or active infections).

4.0 Study Objective

The objective of the study is to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously (SC) in pediatric subjects with moderate-to-severe ulcerative colitis (UC).

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study is designed to enroll 93 subjects (not including the Japanese sub-study) to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

This is a Phase 3, multicenter, randomized, double-blind study designed to evaluate the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in pediatric subjects with moderate to severe ulcerative colitis (UC).

The present study is to confirm the efficacy and safety of adalimumab in pediatric subjects with ulcerative colitis, in accordance with pediatric legislation in EU and US. The study protocol was reviewed and incorporated comments by the PDCO of the EMA and the FDA.

93 pediatric subjects with moderate-to-severe ulcerative colitis (Mayo Score of 6 to 12 points with endoscopy subscore of 2 to 3, confirmed by central reader) will be enrolled at approximately 50 sites worldwide (Section 5.3.1.1).

There also will be up to approximately 9 Japanese subjects in a Japan sub-study to be enrolled at approximately 10 Japan sites. The Japan sub-study will be conducted utilizing the same design as outlined in the main study with the exceptions that are outlined in a separate Japan specific protocol.

The study will allow enrollment of up to 25% of anti-TNF experienced subjects.

Prior to Amendment 4, subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled into the study and randomized 3:2 at Baseline to one of two double-blinded adalimumab induction doses (high induction dose or standard induction dose). The randomization was stratified by Baseline disease severity (Mayo Score [≤ 9 , > 9]), prior exposure to infliximab and corticosteroid use at Baseline.

During the randomized double-blind induction period, subjects assigned to high dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects received adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Subjects randomized to standard dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, adalimumab 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the induction period until Week 8.

At Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) were randomized in a 2:2:1 ratio to one of two adalimumab maintenance treatment groups (standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or high dose [0.6 mg/kg

(maximum dose of 40 mg) every week]) or to placebo, respectively. The randomization was stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) and induction dose.

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the maintenance period until Week 52 and re-randomization to treatment for disease flare will be done according to Amendment 3 stipulations in these subjects.

After Amendment 4, subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and receive open-label (OL) adalimumab high induction dose. During the OL induction period, subjects will receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects will receive adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

At Week 8, subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 and $\geq 30\%$ from Baseline) will be randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) in a 1:1 ratio to one of two adalimumab maintenance treatment groups (standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or high dose [0.6 mg/kg (maximum dose of 40 mg) every week]).

Subjects will receive blinded treatment every week (ew) beginning at Week 8 and will remain on double-blinded therapy through Week 52.

- Subjects who are randomized to standard dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) every other week (eow) and will receive the matching placebo at the alternate week.
- Subjects who are randomized to high dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) ew.
- Subjects who were randomized to placebo prior to Amendment 4 receive matching placebo ew.

At Week 8, subjects who have not achieved a clinical response per PMS will be discontinued from the study. A safety evaluation call will be made 70 days after the last dose of study drug is administered to obtain follow-up information on any ongoing or new adverse events.

The duration of the study could be up to 66 weeks, which includes a Screening Period of up to 28 days, an 8-week induction period and a 44-week double-blind maintenance period and a 70-day follow-up. There is a ± 3 day window for all study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

The Screening period may be extended as necessary after consultation with the AbbVie Medical Monitor for subjects who require initiation of prophylactic anti-TB therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results).

Upon completion of the study, subjects will have the option to enroll into an open-label extension study where they will continue to receive open-label adalimumab.

Efficacy and safety measurements will be performed throughout the study (Section 5.3.1). Clinical evaluation will be at Baseline, Weeks 1, 2, 4, 8, 12, 18, 26, 34, 42, and 52/Premature Discontinuation and unscheduled Visits. Subjects will undergo colonoscopy or flexible sigmoidoscopy during the Screening period and at Weeks 52/Premature Discontinuation Visit to assess disease activity. If the subject underwent an endoscopy within 56 days of Baseline and a video recording of the endoscopy is available, the video recording may be used to assess disease activity and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met, and all technical requirements are fulfilled.

Blood samples for the measurement of adalimumab concentrations will be collected at Baseline, Weeks 2, 4, 8, 12, 26, 34 and 52/Premature Discontinuation Visits and at Unscheduled Visits requiring dose change. Blood samples for measurement of

anti-adalimumab antibodies (AAAs) will be collected at Baseline, Weeks 4, 8, 26 and 52/Premature Discontinuation Visits and at Unscheduled Visits requiring dose change.

Blood samples for measurement of human anti-chimeric antibody (HACA) to infliximab as well as infliximab drug levels will also be collected at Week 0.

Subjects are allowed to be treated with stable doses of UC-related concomitant medications during the study, with the following exceptions and requirements:

- At or after Week 4, subjects taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered based on the investigator's discretion. A proposed tapering schedule is specified in Section 5.3.1.1.
- From Week 4 to Week 12, if the subject should experience an increase in symptoms after corticosteroid was tapered, the subject may have their corticosteroid dose increased back up to the corticosteroid dose at Baseline. This increase must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Subjects who experience disease flare at or after Week 12 are allowed to change their dose or initiate treatment with corticosteroids, immunosuppressants or 5-ASA; these increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities (e.g., leukopenia or elevated liver enzyme) considered moderate to severe in the opinion of the investigator.
- Immunosuppressant therapy may be discontinued at or after Week 12 at the investigator's discretion.

Treatment of Subjects with a Disease Flare During the Study

Criteria for Disease Flare are as follows:

- Subjects with a Week 8 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Week 8 score.

- Subjects with a Week 8 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Week 8 score.

Subjects will be expected to remain on blinded therapy throughout the 44-week maintenance period. However, subjects with a disease flare may be re-randomized to receive the following blinded-treatment at or after Week 12, [Figure 4](#).

- Subjects who are randomized to standard maintenance dose (0.6 mg/kg eow [maximum of 40 mg eow]) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume receiving the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
- Subjects who are randomized to high maintenance dose (0.6 mg/kg ew [maximum of 40 mg ew]) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew).
- Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.

If a subject continues to meet the definition of disease flare (2nd time) following at least a 4-week course of blinded therapy since the subject has been re-randomized for the disease flare, they may be switched to open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg]. *(If a subject was re-randomized at Week 12 (to receive either re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg])), then the earliest that subject could be evaluated to determine if*

they meet the criteria for disease flare for switch to OL (0.6 mg/kg [maximum of 40 mg]) weekly dosing is at Week 16.

If a subject continues to meet the definition of disease flare (3rd time) following a 4-week course of open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab open-label 40 mg ew (maximum dose, not weight based).

Subjects with persistent disease flare while on adalimumab 40 mg ew (max dose) may be withdrawn from the study at the investigator's discretion.

During open-label rescue therapy, subjects who are responders and have been in remission for at least 8 consecutive weeks ($PMS \leq 2$ with no individual subscore > 1) may have their dosage decreased from ew to eow. The investigator should receive prior approval from the Medical Monitor before taking any action with regard to dose de-escalation.

If subjects demonstrate disease flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to adalimumab ew dosing. The investigator should receive prior approval from the Medical Monitor before taking any action with regard to dose re-escalation.

For subjects who meet the criteria for dose change, blood samples (for the determination of adalimumab and AAA concentrations, hs-CRP) will be collected just prior to receiving any dose change (blinded therapy, escape to open-label adalimumab, dose de-escalation and dose re-escalation).

No study drug will be administered or injected at the final visit.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects who end study participation early will have a Termination Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing AEs.

Re-screening

Subjects who initially screen fail for the study may be permitted to re-screen following re-consent. All screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion and none of the exclusion criteria as far as they are assessable at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the assessment of a PPD test, (or equivalent), or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test), chest x-ray (if applicable), x-ray of the wrist and ECG, these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 3 months (90 days) have passed. An endoscopy will not be required to be repeated for re-screening provided that the prior endoscopy confirmed subject's eligibility, the conditions noted in Section 5.3.1.1 are met and no more than 56 days have passed from Baseline.

For subjects in re-screening, lab assessments will not need to be repeated if the time between Screening and Re-screening is less than 28 days.

However, lab assessments will need to be repeated at Baseline if the time between lab assessments during previous Screening and Baseline is greater than 28 days.

Additionally, a PG sample will not be required to be repeated for re-screening provided that a PG sample has already been collected during previous Screening and is still available for analysis. As appropriate, sites are encouraged to contact the AbbVie Medical Monitor to confirm if subjects should or should not be re-screened.

Figure 1. Study Design Schematic Prior to Amendment 4

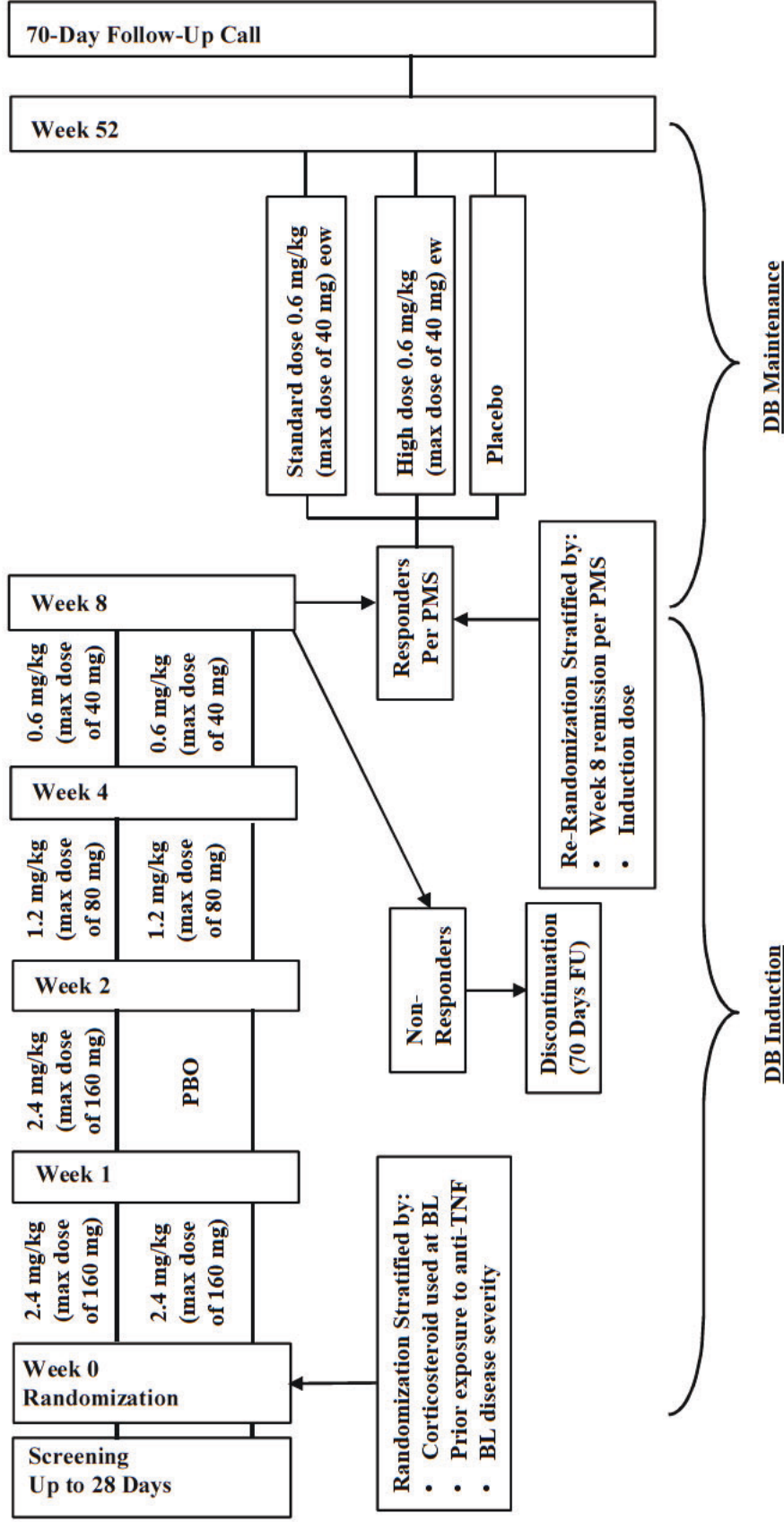


Figure 2. Study Design Schematic After Amendment 4

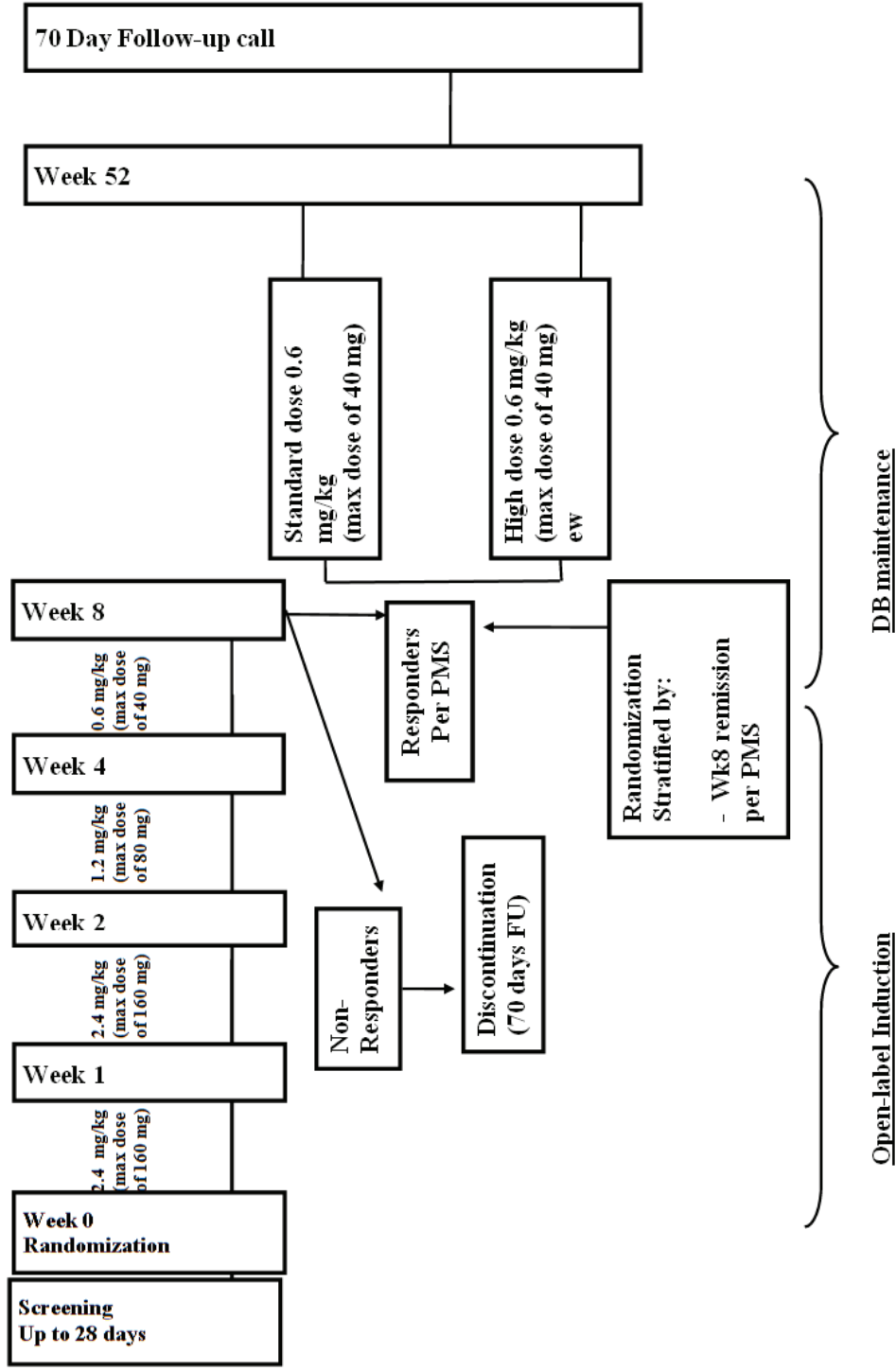
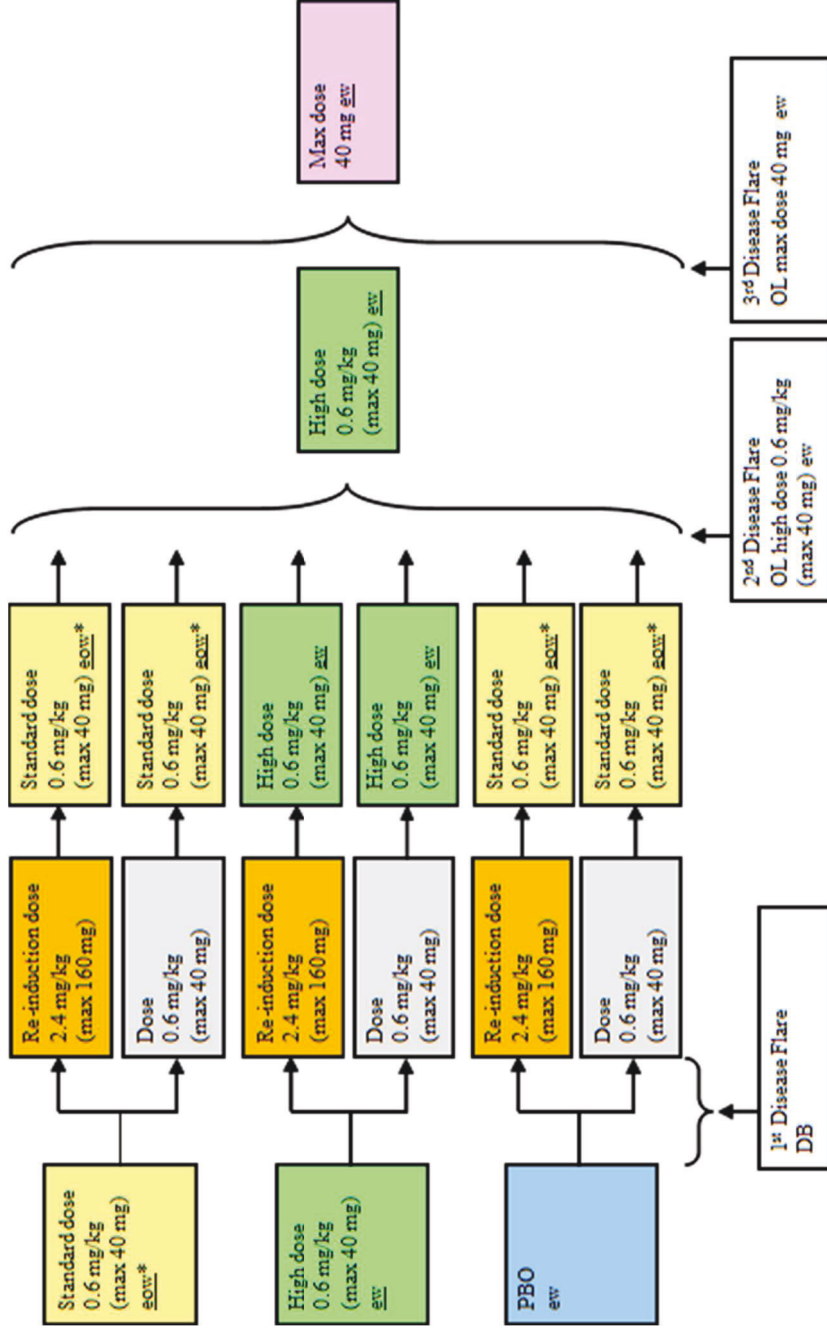
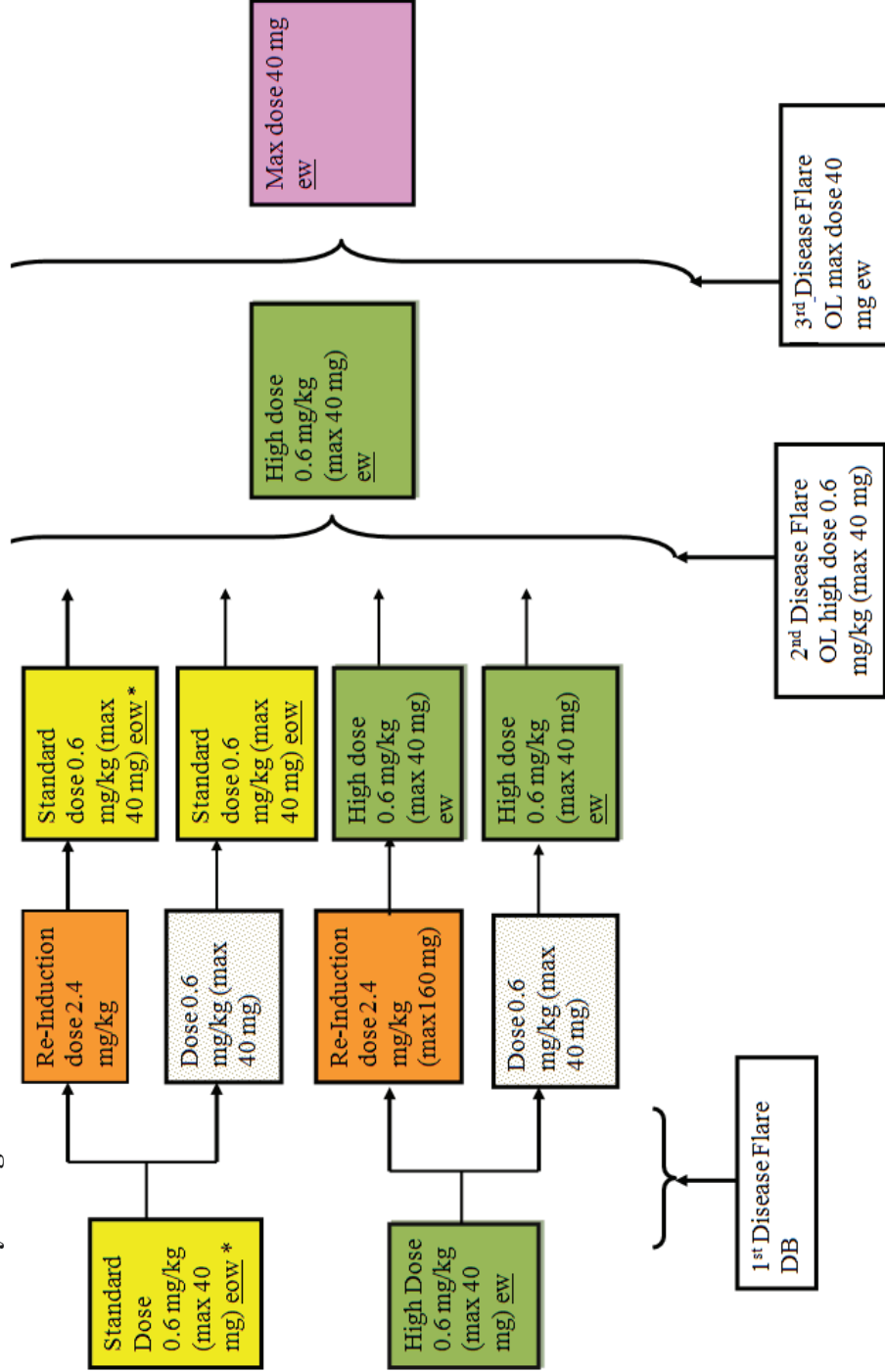


Figure 3. Study Design Schematic for Dose Escalation Prior to Amendment 4



* Subject will receive the matching PBO at the alternate week.

Figure 4. Study Design Schematic for Dose Escalation After Amendment 4



*Subject will receive the matching placebo at the alternate week

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets all of the following:

1. Subjects from the ages of 4 and 17 prior to baseline dosing.
2. Subjects with a diagnosis of UC for at least 12 weeks prior to screening confirmed by endoscopy with biopsy.

A colonoscopy will be performed during the screening period unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis without evidence of dysplasia, colon cancer or infection). In this case the screening endoscopy may be either a colonoscopy or a flexible sigmoidoscopy.

If the subject underwent an endoscopy within 56 days of Baseline and a video recording of the endoscopy is available, the video recording may be used and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met, and all technical requirements are fulfilled.

Note:

- If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must also be performed.
 - Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.
3. Active ulcerative colitis with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) despite concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):

- Oral prednisone of ≥ 2 mg/day or equivalent, but not exceeding 40 mg/day, or oral budesonide ≥ 3 mg/day, but not exceeding 9 mg/day, with a stable dose for at least 7 days prior to Baseline;
and/or
 - At least a consecutive 28 day course of azathioprine or 6-MP or methotrexate (MTX) prior to Baseline, with a stable dose prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of 230 – 450 pmol/ 8×10^8 RBC on the current dosing regimen or MTX ≥ 15 mg/m² body surface area/week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.
Note: If subjects are on both oral corticosteroid and immunosuppressants BOTH of the drugs need to meet the above criteria.
and/or
 - Concurrent therapy with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) is not required for subjects who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.
4. Parent or guardian has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed or before any concomitant medication is discontinued for the purpose of this study. Pediatric subjects will be included in all discussions in order to obtain verbal and/or written assent.

5. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
6. Subject has a negative TB Screening Assessment.

If a subject has a positive (≥ 5 mm induration) PPD test and/or IGRA test at Screening, a CXR (PA and lateral view) must be performed for evaluation of active TB disease. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline (Section 5.3.1).

7. If female, subject who is either not of childbearing potential, defined as premenstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

Examples of approved methods of birth control include the following (see local informed consent for more detail):

- Total abstinence from sexual intercourse;
 - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
 - Hormonal contraceptives for 90 days prior to study drug administration;
 - A vasectomized partner.
8. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

5.2.2 Exclusion Criteria

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

1. Subject with Crohn's disease (CD) or indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.

3. Subjects with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Therapeutic enema or suppository within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of colectomy or subtotal colectomy (with ostomy) or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil, within 30 days prior to Baseline.
7. Female subjects who are breast-feeding or considering becoming pregnant during the study.
8. Positive pregnancy test at Screening or Baseline.
9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subjects on azathioprine or 6-mercaptopurine (6-MP) or MTX and subjects:
 - Have not been on stable doses of these medications for at least 28 days prior to Baseline; or
 - Have discontinued these medications within 28 days of Baseline.
11. Subjects on oral aminosalicylates who:
 - Have not been on stable doses of these medications for at least 14 days prior to Baseline; or
 - Have discontinued use of aminosalicylates within 14 days of Baseline.
12. Subjects on growth hormone who have not been on a stable dose for at least 4 weeks prior to Baseline.
13. Subjects on oral corticosteroids who:
 - Have not been on stable doses of these drugs for at least 7 days prior to Baseline; or
 - Discontinued use of oral corticosteroid within 14 days of Baseline; or

- Have been taking both budesonide and prednisone (or equivalent) simultaneously.
14. Received intravenous corticosteroids within 5 days prior to Screening or during the Screening Period.
 15. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.
 16. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.
 17. Previous treatment with adalimumab or previous participation in an adalimumab clinical study.
 18. Positive *Clostridium difficile* (*C. difficile*) stool assay during the Screening Period.
 19. Currently receiving total parenteral nutrition (TPN).
 20. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
 21. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).
 22. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
 23. Subjects with any active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
 24. Subjects with a positive result for Hepatitis B surface antigen (HBs Ag) or any HBV DNA PCR result that meets or exceeds detection sensitivity will be excluded.
 25. Chronic recurring infections or active TB.

26. Subject has been treated with any investigational drug of chemical or biologic nature or any investigational procedure (including previous fecal transplantation) within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline Visit.
27. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
28. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab [Tysabri[®]] or efalizumab [Raptiva[®]] or rituximab [Rituxan[®]]).
29. Known hypersensitivity to adalimumab or its excipients.
30. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

If the Screening endoscopy shows evidence of dysplasia or malignancy, subject may not be enrolled in the study.
31. Screening laboratory and other analyses show any of the following abnormal results:
 - ECG – with clinically significant abnormalities;
 - Aspartate transaminases (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range;
 - Total bilirubin ≥ 3 mg/dL;
 - Serum creatinine > 1.6 mg/dL;
 - Clinically significant abnormal screening laboratory results as evaluated by the investigator.
32. Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject has received within 30 days prior to Baseline, is receiving at the time of enrollment, or receives during the study, must be recorded in source documents and on the appropriate page of the electronic case report form (eCRF), along with the reason for use, dates of administration including start and end dates, and dosage information including dose, route and frequency.

Any antibiotic that the subject has received within 60 days prior to Baseline, is receiving at the time of enrollment, or receives during the study, must be recorded in source documents and on the appropriate page of the electronic case report form (eCRF), along with the reason for use, dates of administration including start and end dates, and dosage information including dose, route and frequency.

Ulcerative colitis specific medications (including corticosteroids, aminosalicylates and immunosuppressant agents) that the subject has received within 90 days of Baseline should be recorded on the appropriate page of the electronic case report form (eCRF) and should include the dates of administration and dosages.

Subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability will have the last dosage and dates of administration and reasons for discontinuation recorded in appropriate eCRF.

In addition, subjects who failed to respond or were intolerant to treatment with corticosteroids or immunosuppressants within the past 1 year will have the highest previous administered dose recorded in appropriate eCRF.

Prior azathioprine, 6-MP and MTX use (since birth) will be asked. If subjects have/had ever been treated with azathioprine and/or 6-MP and/or MTX, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will be recorded in appropriated eCRF.

For subjects previously treated with biologics (e.g., etanercept and/or infliximab), the biologic therapy history will be recorded, this included the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment with these products should be documented.

The AbbVie study-designated physician identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy.

In addition for subjects 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 eCRF 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 eCRF. 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 eCRF pages.

5.2.3.2 Concomitant Therapy

Subjects may continue their doses of azathioprine, 6-MP or MTX provided they are on these medications for at least 28 days prior to Baseline and that doses have been stable for at least 28 days prior to Baseline. Doses of these concomitant medications (azathioprine, 6-MP or MTX) must remain stable for the first 12 weeks of participation, except in the event of treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the investigator. Immunosuppressant

dose (azathioprine and 6-MP or MTX) can be discontinued starting at Week 12 per investigator's discretion. Subjects who experience disease flare at or after Week 12 are allowed to change their dose or initiate treatment with corticosteroids, immunosuppressants or 5-ASA; these increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.

Subjects may continue doses of aminosalicylates provided they are on these medications for at least 14 days prior to Baseline and that doses have been stable for at least 14 days prior to Baseline. Oral antibiotics are permitted prior to Baseline and subjects may continue these medications provided that they were prescribed for ulcerative colitis but not for treatment of an infection. Corticosteroids are permitted if the subject has been on stable doses prior to Baseline as outlined in inclusion criterion 3 in Section 5.2.1. Subjects are not allowed to change the corticosteroid dose during the first 4 weeks of the study. At or after Week 4, subjects who are taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered off based on the investigator's discretion.

A proposed schedule to taper corticosteroid dose starts with a weekly decrease by 5 mg/day prednisone (or equivalent) for doses > 10 mg/day of prednisone (or equivalent) until a 10 mg/day (or equivalent) dose is reached, then a weekly decrease by 2.5 mg/day (or equivalent) until discontinuation.

A proposed schedule to taper budesonide dose starts with a weekly decrease by 3 mg/day until discontinuation.

From Week 4 to Week 12, if the subject should experience an increase in symptoms after corticosteroid was tapered, the subject may have their corticosteroid dose increased back up to the corticosteroid dose at Baseline. This increase must be discussed with and approved by the Medical Monitor before.

At or after Week 12, if the subject should experience disease flare, the subject may have their corticosteroid dose initiated, reinitiated or increased (as mentioned above). These

initiations, reinitiations or increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.

Subjects may not be on both budesonide and prednisone (or equivalent) simultaneously.

Subjects who enter the study on probiotics may continue this therapy provided the dose remains unchanged.

Subsequent changes in all concomitant medications will be assessed at each study visit from Baseline (Week 0) through Week 52/Premature Discontinuation Visits. All subjects will be given a Subject Medication Log to help track any change in therapy. These changes will be documented in the source documents and captured on the appropriate eCRF page.

All non-UC medications (prescription and over-the-counter) used during the 30 days prior to Baseline will be recorded and must include all doses and date ranges of administration. Vaccines administered to the subject within 30 days prior to Baseline will be listed as a concomitant medication. Any antibiotic used during the 60 days prior to Baseline will be recorded and must include all doses and date ranges of administration.

The AbbVie study Primary Therapeutic MD identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- Biologic therapy with a potential therapeutic impact on ulcerative colitis including but not limited to the following:
 - Anakinra (Kineret[®]);
 - Abatacept (Orencia[®]);
 - Natalizumab (Tysabri[®]);
 - Efalizumab (Raptiva[®]);

- Infliximab (Remicade[®]);
- Etanercept (Enbrel[®]);
- Rituximab (Rituxan[®]);
- Tocilizumab (Actemra[®]);
- Golimumab (Simponi[®]);
- Certolizumab (Cimzia[®]);
- Ustekinumab (Stelara[®]);
- Belimumab (Benlysta[®]);
- Vedolizumab (Entyvio[®]).
- The use of Tofacitinib (Xeljanz[®]) is prohibited during the study.
- Live vaccines (during the study and for 70 days after the last dose of study drug).
- The use of cyclosporine, tacrolimus, or mycophenolate mofetil is prohibited within 30 days prior to Baseline and during the study.
- Rectal therapy with any therapeutic enemas or suppositories is prohibited within 14 days prior to Screening endoscopy, during the remainder of the Screening Period and during the study. Rectal medication for bowel preparation prior to endoscopy is permitted.
- Intravenous corticosteroid use is prohibited within 5 days prior to Screening, during the Screening Period and during the study.
- Any investigational drug of chemical or biologic nature or any investigational procedure (including previous fecal transplantation) are prohibited within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline and during the study.

The AbbVie Primary Therapeutic MD identified in Section 6.1.5 should be contacted if there are any questions regarding prohibited therapy.

5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in [Table 1](#). There is a \pm 3-day window for all study visits.

Table 1. Study Activities

Activity	Ser	Baseline (Wk 0) ^a	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26	Wk 34	Wk 42	Wk 52/ Premature Discontinuation	Unscheduled Visit	70 Day Follow-up Phone Call ^w
Informed Consent	X													
Inclusion/Exclusion	X	X												
Medical/Surgical History	X	X												
Tobacco and Alcohol Use	X													
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	
Endoscopy ^{c,d}	X ^c											X ^d		
Physical Examination ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	
TB Screening ^f	X											X ^h		
Chest X-ray ^g	X ^g											X ^h		
ECG ⁱ	X													
Chemistry and Hematology ^j	X	X ^k		X	X	X	X	X	X	X	X	X	X	
Urinalysis ^l	X	X ^k		X	X	X	X	X	X	X	X	X	X	
Pregnancy Tests ^m	X ^m	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	X ⁿ	
<i>C. difficile</i> toxin	X													

Table 1. Study Activities (Continued)

Activity	Scr	Baseline (Wk 0) ^a	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26	Wk 34	Wk 42	Wk 52/ Premature Discontinuation	Unscheduled Visit	70 Day Follow-up Phone Call ^w
ANA/dsDNA ^o	X													
HBV Screening	X ^z													
Infliximab and HACA Concentration		X												
Adalimumab Concentration ^{p,q}		X	X	X	X	X	X	X	X	X	X	X	X ^q	
AAA Concentration ^{p,q}		X			X	X			X			X	X ^q	
hs-CRP ^q		X		X	X	X	X	X	X	X	X	X	X ^q	
PUCAI		X	X	X	X	X	X	X	X	X	X	X	X	
Partial Mayo Score		X	X	X	X	X	X	X	X	X	X	X	X	
Mayo Score		X										X		
IMPACT III Questionnaire ^r		X				X			X			X		
Work Productivity and Impairment Questionnaire (WPAI): UC – Caregiver ^s		X	X	X	X	X	X	X	X	X	X	X		
Tanner Stage ^y	X								X					
X-ray for Bone Age	X ^{ae}											X		
Anthropometric Evaluations		X						X				X		
PG (optional) ^x		X												

Table 1. Study Activities (Continued)

Activity	Scr	Baseline (Wk 0) ^a	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26	Wk 34	Wk 42	Wk 52/ Premature Discontinuation	Unscheduled Visit	70 Day Follow-up Phone Call ^w
Serologic Markers/mRNA (optional) ^{aa}		X				X			X			X		
mRNA (optional) ^{ad}		X				X			X			X		
Corticosteroid Taper ^t					X	X	X	X	X	X	X		X	
Monitor Adverse Events ^u		X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Diary Dispensing/ Reviewing ^{ac}	X ^{ab}	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Administration ^v		X	X	X	X	X	X	X	X	X	X		X ^v	

Scr = Screening

- a. The Baseline visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits. Medical/surgical history at Baseline is an update since Screening.
- b. Vital sign determinations of weight, sitting blood pressure, pulse rate, respiratory rate, body temperature will be obtained at each visit.
- c. A colonoscopy will be performed during screening unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate documentation for both colonoscopy are available (to confirm the diagnosis and no evidence of dysplasia, colon cancer or infection). In this case the screening endoscopy may be either a colonoscopy or a flexible sigmoidoscopy. If the subject underwent an endoscopy within 56 days of Baseline and the video recording of endoscopy is available the video recording may be used and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met, and all technical requirements are fulfilled. If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must be performed. Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.

Table 1. Study Activities (Continued)

- d. At Week 52, a colonoscopy or flexible sigmoidoscopy will be performed. In patients who prematurely discontinue, a colonoscopy or flexible sigmoidoscopy will only be performed if premature discontinuation occurs after Week 26.
- e. Physical examinations performed at Screening, Baseline, Week 26, and Week 52/Premature Discontinuation Visits are full physical examinations and those performed at all other visits are symptom based.
- f. Subjects with negative PPD test and/or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) within 90 days of Screening would not require a repeat test, if all protocol required documentation is available, provided nothing has changed in the subject's medical history to warrant a repeat test. PPD skin test is to be read 48 to 72 hours after placement.
- g. All subjects with a positive PPD test or positive Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) will undergo a standard CXR (posterior-anterior [PA] and lateral views) at the Screening Visit to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal chest x-ray within 90 days of Screening, provided all protocol required documentation is available at the site.
- h. For subjects with a negative TB test at Screening, TB test will be required at Week 52. If the annual TB screen is positive, a CXR may be required for evaluation of active TB. An annual TB screen testing will not be required for subjects who have been treated for latent or active TB or have had a positive TB test at any time (prior to the study, Screening, or testing performed at any time point during the study). For such subjects, annual evaluation by a physician for clinical signs/symptoms of active TB (including a directed TB history and physical exam including lungs, lymph nodes and skin) or newly identified TB risk factors will be required at Week 52.
- i. Subjects with normal ECG within 90 days of Screening would not require a repeat ECG, if documentation is available.
- j. Blood draws should be performed after completion of all clinical assessments and questionnaires.
- k. Lab assessments will only need to be repeated at Baseline if the time between Screening lab assessments and Baseline is greater than 28 days, or any new concomitant medication with potential impact on laboratory parameters was started during the Screening Period. For subjects in re-screening lab assessments will not need to be repeated if the time between Screening and Re-screening is less than or equal to 28 days. However, lab assessments will need to be repeated at Baseline if the time between lab assessments during previous Screening and Baseline is greater than 28 days.
- l. Dipstick urinalysis will be completed by the sites at all required visits. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.
- m. All females of childbearing potential will have a serum pregnancy test at Screening, and Week 52/Premature Discontinuation Visit.
- n. At the Baseline and all subsequently scheduled study visits, all females of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study. Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities.

Table 1. Study Activities (Continued)

- o. Anti-dsDNA performed if ANA result is positive.
- p. Blood samples for the measurement of adalimumab and AAA concentrations will be collected prior to dosing at the said weeks of sampling.
- q. Blood samples (for measurement of serum adalimumab and AAA concentrations and hs-CRP) will be collected for subject just prior to any dose change (blinded therapy, escape to open-label, dose escalation, dose de-escalation and re-escalation).
- r. IMPACT III Quality of Life questionnaire at Baseline, Weeks 8, 26 and 52/Premature Discontinuation Visit will be completed for subjects 9 or older at the baseline study visit.
- s. WPAI will be completed by subject's parent or legal guardian at every visit except the Unscheduled Visit. The questionnaire will not be completed if the subject's parent or legal guardian is not taking care of the subject anymore.
- t. Subjects may begin corticosteroid taper at Week 4, based on the investigator's discretion.
- u. Collection of SAEs begins the day the subject signs the informed consent.
- v. Study drug may be dispensed at the Unscheduled Visit if there is a change in the dosing schedule (i.e., subject meets criteria of disease flare) or if damaged drug needs replacement.
- w. Site personnel will contact all subjects approximately 70 days following study drug discontinuation to determine the occurrence of AEs or SAEs.
- x. Verify subject has signed consent for optional pharmacogenetic sample. If the sample is not collected at Baseline, it may be collected at any time during the study. If the sample was collected at Screening visit, no PG sample should be collected at Baseline.
A PG sample will not be required to be repeated for re-screening provided that a PG sample has already been collected during previous Screening and is still available for analysis.
- y. Tanner Stage will be assessed at Screening (or at Baseline as appropriate), Week 26 and 52/Premature Discontinuation Visit if premature discontinuation occurs after Week 26.
- z. Subjects will be tested for the presence of Hepatitis B Virus (HBV) at Screening. A positive result for the Hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for HBs Ab and HBc Ab Total. Subjects who are HBs Ag (-), HBs Ab (-), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary. Subjects with a negative HBs Ag test and tests showing the results below, do not require HBV DNA PCR qualitative testing.
 - HBc Ab Total (-) and HBs Ab (-)
 - HBc Ab Total (-) and HBs Ab (+)
 - HBc Ab Total (+) and HBs Ab (+)

Table 1. Study Activities (Continued)

- aa. If subject has signed consent for optional serologic markers, blood samples will be collected at Baseline, Week 8, 26 and 52/Premature Discontinuation Visit.
- ab. Subjects will be dispensed a subject diary at Screening and will be trained on how to complete the diary by site staff during the Screening visit.
- ac. All subjects should complete their subject diary on a daily basis throughout the entire study, including if and when hospitalized whenever possible. The diary will be reviewed by site personnel with the subject at each visit and collected at the Week 52/Premature Discontinuation Visit.
- ad. If subject has signed consent for optional mRNA, blood samples will be collected at Baseline, Week 8, 26 and 52/Premature Discontinuation Visit.
- ae. An x-ray of the wrist at Screening will not be required if the subject had an x-ray within 90 days of Screening, provided all protocol required documentation is available. An x-ray of the wrist will not be required at a Premature Discontinuation visit. 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 can be omitted.

5.3.1.1 Study Procedures

The study procedures outlined in [Table 1](#) are discussed in detail in this section, with the exception of drug concentration measurements and antibody measurements (discussed in [Section 5.3.2](#)), and the collection of adverse event (AE) information (discussed in [Section 6.1.4](#)). All study data will be recorded in source documents and on the appropriate eCRFs.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria at both the Screening and Baseline Visits.

Informed Consent

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific informed consent will be reviewed, signed and dated by the parent or their guardian before any study procedures are undertaken, or before any concomitant medications are withheld from the subject in order to participate in this study. Pediatric subjects will be included in all discussions. If a subject becomes of legal age in the state of residence during the course of the study, an informed consent will need to be obtained at that time. Additionally, in complying with each institution's IRB requirements, an informed assent may also be obtained from the subject.

Details about how informed consent will be obtained and documented are provided in [Section 9.3](#).

Before informed consent may be obtained, the investigator or designee will explain the nature and purpose of the study and its procedures to the subject. Ample time and opportunity for the subject or the parent or their guardian, or the subject's legally acceptable representative to ask any questions about the study will be provided, so that an informed consent can be made as to whether or not to participate in the study. All questions about the study will be answered to the satisfaction of the subject.

After the informed consent is signed and dated by the parent or guardian, the person who discussed the informed consent will also sign and date the document and provide a copy of the informed consent to the subject. The original informed consent will be placed in the subject's medical record with documentation that the informed consent was signed prior to the performance of any study procedures and that the subject was given a signed and dated copy.

Medical and Surgical History

A complete medical and surgical history (which includes family history and UC-onset date) as well as history of tobacco and alcohol use, will be obtained from each subject during the Screening Period. The date of the most recent endoscopy requiring bowel preparation prior to Screening will be asked. An updated medical history will be obtained at the Baseline Visit to ensure that the subject still qualifies.

Prior azathioprine, 6-MP or MTX use (since birth) will be asked. If subjects have/had ever treated with azathioprine and/or 6-MP and/or MTX, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment with azathioprine and/or 6-MP and/or MTX will be recorded in appropriated eCRF.

A detailed medical history with respect to TB exposure needs to be documented. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, body weight, and body temperature will be obtained at each visit. Blood pressure, pulse rate and respiratory rate should be performed before blood draws are performed. All measurements will be recorded in metric units if possible.

TB Screening

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or a Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

If a subject had a negative PPD test or IGRA test within 90 days prior to Screening, and all protocol required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases 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 (or according to manufacturer's guide) after placement 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 induration must be recorded in mm not as positive or negative. The absence of induration should be recorded, as "0 mm," not "negative." *(If required by specific countries a two-step test may be performed per local guidelines. The result of the second test should be recorded. An induration of 5 mm or greater will be considered as PPD positive.)*

Subjects who have had an ulcerating reaction to PPD skin test in the past should not be re-exposed and should not be tested at Screening but will be considered PPD positive.

If there are sites where the accepted testing materials are not available, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.

In the assessment of the CXR a radiologist must note the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, (3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator must contact the AbbVie Medical Monitor before enrolling the subject.

If the PPD or the IGRA test is positive or the subject has a CXR indicative of latent TB, the subject will be required to initiate and have taken at least 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of Centers for Disease Control and Prevention (CDC) recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy. The Screening period may be extended as necessary for subjects who require initiation of prophylactic anti-TB therapy.

Subjects with a prior history of latent TB that have a documented completion of the CDC recommended or local guideline recommended prophylaxis may be permitted to enroll. If the subject has a prior history of latent TB but has not completed or received prophylaxis, prophylaxis must be initiated for at least 2 weeks (or per local guidelines, whichever is longer) before enrolling into the study and must be continued until completion as per CDC recommendation.

If the subject has a prior history of active TB they must have documentation of completion of CDC recommended or local guideline recommended treatment and documentation of resolution of the infection.

In the event both a PPD test and IGRA test are performed, the result of the IGRA test will supersede the result of the PPD test. If the IGRA test is indeterminate, the site should repeat the test with another blood sample or perform a PPD test. If the second IGRA test is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis.

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

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 Tuberculosis 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 or the IGRA test and the chest x-ray and has to give his/her opinion about the eligibility of each subject to be enrolled to the study. This opinion must be documented in writing in the subject's source documents.
- All subjects with a positive PPD or IGRA test need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie medical monitor and all such subjects need to receive prophylaxis for latent Tuberculosis. Under no circumstances can a subject with a positive PPD or IGRA test result and no prior history of treatment for active or latent Tuberculosis be allowed into this trial.

Annual TB Testing

For subjects with a negative TB test at Screening, either an annual PPD or IGRA test will be required for any subject participating in the trial at Week 52 (Table 1). If the annual TB screen is positive (PPD is positive or the IGRA test is positive), a CXR may be required for evaluation of active TB. For any subject with a positive annual TB screen, the site should contact the AbbVie Medical Monitor for further discussion. Subjects found to have latent TB, will be required to start a course of CDC recommended prophylaxis or prophylaxis per local guidelines as soon as possible. Subjects found to

have active TB must discontinue study drug and receive CDC recommended or local guideline recommended treatment. Any positive TB screen after the subject has started the study, should be reported as an AE.

An annual TB screen with PPD or IGRA testing will not be required for subjects who have been treated for latent or active TB or have had a positive TB test (PPD or IGRA) at any time (prior to the study, Screening, annual evaluation, or testing performed at any time point during the study). For such subjects, annual evaluation by a physician for clinical signs/symptoms of active TB (including a directed TB history and physical exam including lungs, lymph nodes and skin) or newly identified TB risk factors will be required at Weeks 52 (Table 1). For any subject with clinical signs/symptoms of active TB or newly identified TB risk factors, a CXR may be required for evaluation of active TB, and it is recommended to contact the Medical Monitor for further guidance. Subjects with a confirmed active TB should be discontinued from the study and receive standard of care.

Chest X-ray (CXR)

All subjects with a positive PPD test or positive Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) will undergo a standard CXR (posterior-anterior [PA] and lateral views) at the Screening Visit to rule out the presence of TB or other clinically relevant findings. In the event both a PPD test and IGRA test are performed, a CXR will only be required if the IGRA test is positive. The CXR will not be required if the subject had a previous normal chest x-ray within 90 days of Screening, provided all protocol required documentation is available at the site.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator.

Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at Screening in Table 1. A qualified physician will interpret, sign, and date each ECG.

The global interpretation using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible CRA and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol required documentation is available. If there are other findings that are clinically significant, the Principal Investigator must contact the Medical Monitor before enrolling the subject.

Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

Physical Examination

A full physical examination will be performed at Screening, Baseline, Week 26 and Week 52/Premature Discontinuation Visits. Symptom-based physical examinations will be performed at all other visits.

A physical exam will be performed at the designated study visits in [Table 1](#).

Physical examination findings that are related or part of each subject's medical history should be captured on the appropriate eCRF page.

Hepatitis B Testing

All subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening. A positive result for the Hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and

core antibodies (HBc Ab Total). Subjects who are HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing the results below do not require HBV DNA PCR qualitative testing.

- HBc Ab Total (–) and HBs Ab (–)
- HBc Ab Total (–) and HBs Ab (+)
- HBc Ab Total (+) and HBs Ab (+)

Pregnancy Tests

A serum pregnancy test will be performed at the Screening and Week 52/Premature Discontinuation Visits on all female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Investigator or who are of childbearing potential. At the Baseline Visit and all subsequently scheduled study visits, subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Investigator or are of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in [Table 2](#) at the Screening, Baseline, Weeks 2, 4, 8, 12, 18, 26, 34, 42 and 52/Premature Discontinuation Visits. Blood draws should be performed after all clinical assessments and questionnaires, vital sign determinations are obtained and before study drug administration during a visit.

Lab assessments will only need to be repeated at Baseline if the time between Screening lab assessments and Baseline is greater than 28 days.

For subjects in re-screening lab assessments will not need to be repeated if the time between Screening and Re-screening is less than or equal to 28 days. However, lab assessments will need to be repeated at Baseline if the time between lab assessments during previous Screening and Baseline is greater than 28 days.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples.

C. difficile

During the Screening Period, a stool sample will be collected and sent to the central laboratory for testing. The sample will be assessed for the presence of *C. difficile* toxin.

The AbbVie Medical Monitor should be contacted to determine if subjects who had a positive *C. difficile* test at Screening and were treated appropriately, are eligible for re-screening.

The sample must be shipped to the central laboratory using dry ice. Additional information is available in the Investigator Manual provided by the central laboratory.

ANA/anti dsDNA

Blood samples for antinuclear antibody (ANA) will be obtained at Screening. Anti-double-stranded DNA (anti dsDNA) assessments will be performed if ANA is positive.

In the event that subject develops Lupus-like symptoms, ANA and anti dsDNA samples will be obtained.

hs-CRP

Blood samples for high-sensitivity C-Reactive Protein (hs-CRP) will be obtained at the Baseline, Weeks 2, 4, 8, 12, 18, 26, 34, 42 and 52/Premature Discontinuation Visits.

Blood draws should be performed after all clinical assessments and questionnaires, vital sign determinations are obtained and before study drug administration during a visit.

The hs-CRP sample will be collected prior to dose change (blinded therapy, escape to receive open-label drug, dose escalation, dose de-escalation and dose re-escalation).

Urinalysis

Urine samples will be obtained and sent to the central lab for the tests listed in [Table 2](#) at the Screening, Baseline, Weeks 2, 4, 8, 12, 18, 26, 34, 42 and 52/Premature Discontinuation Visits. Microscopic urinalysis will only be performed by the central laboratory if the dipstick UA results are abnormal, where abnormal is defined as a ketone, protein, blood or glucose value of greater than a trace.

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis ^a
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total bilirubin	pH
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein
Neutrophils	Serum glutamic-oxaloacetic transaminase (SGOT/AST)	Blood
Bands	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	Others
Monocytes	Potassium	High-sensitivity C-reactive protein (hs-CRP)
Basophils	Calcium	Antinuclear antibody (ANA)
Eosinophils	Inorganic phosphorus	Anti-double-stranded DNA (anti-dsDNA) – <i>if ANA positive</i>
Platelet count (estimate not acceptable)	Uric acid	β-HCG
	Cholesterol	HBV
	Total protein	<i>C. difficile</i> toxin
	Glucose	
	Triglycerides	
	Albumin	
Additional Blood Samples Collected		
Pharmacokinetic		
Pharmacogenetic (optional)		
Serologic biomarkers and cytokines (optional)		
mRNA (optional)		

a. Microscopic urinalysis will be analyzed when dipstick results are abnormal.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained at Screening and at Week 52/Premature Discontinuation visit to determine changes in bone maturation. Sites should use the Greulich and Pyle method for reading the x-ray.²⁰ The x-ray report requires the signature of the radiologist who read the films or of the investigator. The bone age that is determined by the x-ray should be recorded on the eCRF. Assessment of bone age will not be required for subjects with the Premature Discontinuation visit at or before Week 26. An x-ray of the wrist for the assessment of bone age at Screening will

not be required if the subject had an x-ray within 90 days of Screening, provided all protocol required documentation is available at the site.

Anthropometric Evaluations

Height and weight obtained at Baseline, Week 26 and Week 52/Premature Discontinuation 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.

At Baseline, height from 6 months prior to Screening and maximal weight attained within preceding 6 months will be recorded.

Tanner Stage

Tanner Stage will be assessed at Screening (or at Baseline as appropriate), Week 26 and Week 52/Premature Discontinuation Visit if premature discontinuation occurs after Week 26. Tanner Staging should be captured on the appropriate eCRF page.

Pediatric Ulcerative Colitis Activity Index (PUCAI)

A PUCAI score will also be calculated at all study visits beginning at Baseline.

An example of the PUCAI is located in [Appendix C](#).

The PUCAI score will be assessed using subject-reported symptoms and activity level. The answers should reflect symptoms and activity level during the previous 24 hours. The PUCAI scores of the last 2 days prior to each study visit will be averaged and used for the PUCAI scores for each study visit. The total PUCAI score will be rounded up to the next 5-point interval as applicable. In order to account for unavailable or excluded diary entries as per the provisions given below diary entries for the PUCAI score of the most recent 2 days within 10 days prior to each study visit will be used.

Diary entries of the following days should not be included in the 2 days prior to the visit that are evaluated for the PUCAI score: (1) the day the subject received medication for

bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 2 days prior to the respective study visit.

The subscore for the number of stools per 24 hours during days which a subject received anti-diarrheal medication will be scored as 15.

Mayo Score

The following definitions will be used:

Table 3. Definitions

Term	Definition
Mayo Score	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3), rectal bleeding (0 – 3), physician's global assessment (0 – 3) and endoscopic subscore (0 – 3). This score ranges from 0 – 12 points with higher scores representing more severe disease.
Partial Mayo Score	Composite score of UC disease activity based on the subscores of stool frequency, rectal bleeding, and physician's global assessment and DOES NOT include the endoscopic subscore. This score ranges from 0 – 9 points.
9 point Mayo Score (without SFS)	Composite score of UC disease activity based on the subscores of rectal bleeding (0 – 3), physician's global assessment (0 – 3) and endoscopic subscore (0 – 3). This score ranges from 0 – 9 points with higher scores representing more severe disease.
9 point Mayo Score (without PGA)	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3), rectal bleeding (0 – 3), and endoscopic subscore (0 – 3). This score ranges from 0 – 9 points with higher scores representing more severe disease.
9 point Mayo Score (without RBS)	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3), physician's global assessment (0 – 3) and endoscopic subscore (0 – 3). This score ranges from 0 – 9 points with higher scores representing more severe disease.
6 point Mayo Score (without SFS and endoscopy subscore)	Composite score of UC disease activity based on the subscores of rectal bleeding (0 – 3) and physician's global assessment (0 – 3). This score ranges from 0 – 6 points with higher scores representing more severe disease.
6 point Mayo Score (without PGA and endoscopy subscore)	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3) and rectal bleeding (0 – 3). This score ranges from 0 – 6 points with higher scores representing more severe disease.
6 point Mayo Score (without RBS and endoscopy subscore)	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3) and physician's global assessment (0 – 3). This score ranges from 0 – 6 points with higher scores representing more severe disease.

All subjects will be provided with a Subject Diary at the Screening Visit where they will record ulcerative colitis related symptoms. The Partial Mayo Score will be calculated from the subject diary at each visit beginning at Baseline. The average entry from the 5 days prior to each study visit will be used for each subject-reported subscore. In addition to the physical examination, the investigator should use the subject-reported subscores of abdominal discomfort and functional assessment to determine the physician's global assessment subscore.

Normal number of bowel movement is the number of stools per day (24 hours) that is typical for the subject when having active UC but not experiencing a flare. Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.

The Mayo Score (consisting of the Partial Mayo Score plus the endoscopic subscore) will be calculated at weeks where endoscopy is performed (i.e., Week 0 and Week 52). The endoscopy score used in the calculation of the Mayo Score at Week 0 (Baseline) will be from the Screening endoscopy. The Mayo Score and the Script for collection of Mayo Score are described in [Appendix D](#).

The average stool frequency subscore, rectal bleeding subscore, Partial Mayo Score and Mayo Score for each study visit will be recorded in the eCRF in decimal numbers.

For the purpose of disease flare assessment, Week 8 PMS will be rounded up or down to the nearest full number. *For example, if a patient had a PMS of 5.4 at Week 8 and came in for a disease flare assessment, then the Week 8 PMS would be rounded down to 5.0 for this purpose. If a patient had a PMS of 5.5 at Week 8 and came in for a disease flare assessment, then the Week 8 PMS would be rounded up to 6.0.*

Whenever possible, the same physician (investigator or subinvestigator) should determine all Mayo Scores and Partial Mayo Scores for an individual subject through the duration of the study.

In addition, all endoscopies will undergo a central review process.

IMPACT III Questionnaire²³

Subjects ≥ 9 years old at Baseline will complete an IMPACT III questionnaire at Baseline, Week 8, Week 26 and Week 52/Premature Discontinuation Visit.

WPAI Questionnaire

Work Productivity and Activity Impairment Questionnaire (WPAI) will be completed at every visit except the Unscheduled Visit ([Appendix F](#)).

The subject's parent or legal guardian will complete the WPAI. The questionnaire will not be completed if the subject's parents or legal guardian do/does not take care of the subject anymore.

Corticosteroid Therapy

At or after Week 4, subjects taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered based on the investigator's discretion. Following is the proposed tapering schedule:

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

From Week 4 to Week 12, if the subject should experience an increase in symptoms after corticosteroid was tapered, the subject may have their corticosteroid dose increased back up to the corticosteroid dose at Baseline. This increase must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.

At or after Week 12, if the subjects should experience disease flare, the subjects may have their corticosteroid dose initiated, reinitiated or increased above the corticosteroid dose at Baseline. These initiations, reinitiations or increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.

Immunosuppressant Therapy

At and after Week 12, subjects who are on immunosuppressant (azathioprine, 6-MP or MTX) and have experienced a significant improvement in their clinical response are permitted to discontinue their dose according to the investigator's discretion.

At or after Week 12, if the subject should experience a loss of clinical response the subject may have their immunosuppressant dose increased, initiated or reinitiated with immunosuppressants. These increases, initiations or re-initiations must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.

Subject Diary/Dosing Log

Subjects will be dispensed an electronic diary at Screening and will be trained on how to complete the diary by site staff during the Screening visit. All subjects should complete their subject diary on a daily basis throughout the entire study. The diary will be reviewed by site personnel with the subject at each visit and collected at the Week 52/Premature Discontinuation Visit.

Subjects will also be trained on how to complete the dosing log by site staff. Dosing log must be recorded each time a dose is administered. In the dosing log, the date and time study drug administration, the kit number, vial number and the dose administered will be recorded. At every site visit, the site staff will record subject's body weight and will inform the subject or his/her caregivers about the amount of study drug to be administered each week until the next site visit.

Guidelines for Body Weight Adjusted Volumes of Study Drug for Administration of Induction and Maintenance doses are listed under [Appendix H](#):

- **Appendix H, Part 1** provides the guidelines for body weight adjusted volume for administration of Induction Dose at BL and Week 1.
- **Appendix H, Part 2** provides the guidelines for body weight adjusted volume for administration of Induction dose at Week 2.
- **Appendix H, Part 3** provides the guidelines for body weight adjusted volume for administration of study drug at Weeks 4 and 6.
- **Appendix H, Part 4** provides the guidelines for body weight adjusted volume for administration of study drug starting at Week 8 to Week 51.

Please note, the tables contained in Parts 2, 3, and 4 are also broken down by the weight of the subject, and will provide guidance for whether 1 or 2 vials shall be administered.

Guidelines for Body Weight Adjusted Volumes of Study Drug for Administration of Dose After Re-Randomization for Disease Flare and of OL Adalimumab are listed in [Appendix I](#) and [Appendix J](#), respectively.

- [Appendix I](#) provides the guidelines for body weight adjusted volume for administration of dose after re-randomization for disease flare (First disease flare).
- [Appendix J](#) provides the guidelines for body weight adjusted volume for administration of OL drug (Second disease flare).

The dosing records will be reviewed and verified for compliance at each visit by the research personnel at the study center and reinforced if necessary. 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 the source documents and in the appropriate drug accountability form.

The subject should bring the subject diary/dosing log to every study visit.

Study Drug Dispensing/Administration

Study drug will be administered to all subjects onsite by either site medical staff, the subjects or designee (friend, family member or healthcare professional) during all the visits from Baseline through Week 4. Subject or a designated family member or friend will be given instructions on subcutaneous injection administration during these first four site visits.

Injections during subsequent study visits will be performed at the site by the subject or their designated family member or friend under the supervision of site medical staff to reinforce proper aseptic subcutaneous injection technique. Subjects or a trained

designated family member or friend or will perform the injections of the study medication in the subject's home during the weeks when a clinic visit is not scheduled.

At all office visits, subjects should be observed after study drug administration until judged medically appropriate by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication 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.

Subjects should administer study medication on the same day of the week. The dosing dates for all doses of study drug should be calculated from the Baseline visit date. A \pm 3-day window is allowable for scheduled study dosing dates. For subjects who 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 \pm 3-day window, please contact the AbbVie Medical Monitor for additional instructions.

Study drug kits will be assigned by the IVRS/IWRS. Since the amount of study drug that subject gets based on subject's body weight, at every site visit, study personnel will record subject's weight and will inform subject the amount of study drug to be administered.

Subjects will be instructed to return all used and unused syringes, Sharps containers and empty boxes at each visit for accountability.

Endoscopy

An endoscopy will be performed on the following occasions:

- During Screening
- Week 52/Premature Discontinuation

A colonoscopy will be performed during the Screening period unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate endoscopy documentation is available (to confirm the diagnosis and extent of disease and no evidence of dysplasia, colon cancer or infection as per review by the investigator). In this case the screening endoscopy may be either colonoscopy or a flexible sigmoidoscopy.

If the subject underwent an endoscopy within 56 days of Baseline and a video recording of endoscopy is available, the video recording may be used and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met, and all technical requirements are fulfilled.

Note:

- If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must also be performed.
- Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.

The endoscopy during the Screening period (or video recording of endoscopy within 56 days of Baseline) will be used to provide the endoscopy subscore for calculating the Mayo Score at Baseline. If, in the assessment of the endoscopist, the Screening endoscopy does not indicate an endoscopy subscore of 2 or 3 per eligibility requirements, the subject should be screen-failed and the video should not be sent for central review. Additionally, if the investigator determines that the subject is not eligible because an inclusion criterion is not fulfilled or an exclusion criterion is met for any other reason the video should not be sent for central review.

At Week 52/Premature Discontinuation Visit, subjects will undergo either colonoscopy or flexible sigmoidoscopy for evaluation of mucosal healing. The evaluation will be done by usage of the endoscopy subscore scale of the Mayo Score. Endoscopies will include an assessment of friability.

If subjects prematurely discontinue from the study before or at Week 26, the endoscopy at the Premature Discontinuation Visit will not be required.

All endoscopies will be recorded and will be reviewed by a central reviewer who is blinded to the therapy. The central reviewer will assess the endoscopy subscore. The endoscopy subscore result from the central reviewer will be used to evaluate the eligibility of a subject for the study, as well as to evaluate mucosal healing at Week 52.

Discrepancies between the central reviewer and the site endoscopist regarding a subject's score and eligibility will be finally judged through adjudication by a second central reviewer. The adjudicator will not provide an assessment but will select the assessment with whom he/she agrees. The adjudicator's assessment will be considered final.

The endoscopy subscore will be reviewed by the endoscopist at the site for each endoscopy and the site endoscopist will document the endoscopy subscore and friability status in subject's source. The site's endoscopy subscore will be noted in the database but the central reviewer's endoscopy subscore will be used for the efficacy analyses.

The same endoscopist should perform all endoscopies for an individual subject throughout the study. In addition, where possible, the investigator or subinvestigator should be the endoscopist for the study.

For re-screening, an endoscopy will not be required to be repeated provided that the prior endoscopy confirmed subject's eligibility, the conditions noted above are met and the date of the prior endoscopy is within 56 days from Baseline.

Biopsy During Endoscopy

During the Screening Period and at the Week 52/Premature Discontinuation Visit, biopsy samples may be taken at the investigator's discretion and evaluated by a qualified local pathologist and the results reviewed by the investigator to confirm the diagnosis and no evidence of dysplasia/malignancy or infection. If no appropriate documentation for confirmation of the diagnosis is available from previous biopsy reports as per the investigator's judgment a diagnostic biopsy must be performed. The signed pathology

report will be monitored by the responsible CRA and kept with the subject's source documents onsite. Subjects would not be enrolled if colon dysplasia or colon cancer is discovered at Screening endoscopy. If a diagnosis of colon dysplasia or colon cancer or an infection is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be recorded as an adverse event and the subject should be discontinued from the study.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis (Optional)

One 2 mL whole blood sample for DNA isolation will be collected at the Baseline Visit from each subject who consents for pharmacogenetic analysis. If the sample is not drawn at the Baseline visit, it may be drawn at any other visit during the study. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. Specific instructions for preparation and storage of DNA samples will be provided by the central laboratory, the Sponsor, or its designee.

A PG sample will not be required to be repeated for re-screening provided that a PG sample has already been collected during previous Screening and is still available for analysis.

AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for no longer than 20 years after completion of the study (where allowed by local regulations) for possible future research.

The site or the subject will not receive the results of the genetic analysis.

5.3.1.3 Blood Samples for Serologic Markers and Cytokine Analysis (Optional)

One 4 mL of blood sample for serologic markers and cytokines analysis will be collected at the time points indicated in Table 1, from each subject who consents for serologic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. Specific instructions for preparation and storage of samples for serologic

markers and cytokines will be provided by the central laboratory, the Sponsor, or its designee.

Sample will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for up to 20 years (where allowed by local regulations) after completion of the study research.

The site or the subject will not receive the results of the serologic markers and cytokine analysis.

5.3.1.4 Blood Samples for mRNA Analysis (Optional)

One 2.5 mL of blood sample for mRNA analysis will be collected at the time points indicated in [Table 1](#), from each subject who consents for optional analyses. The procedure for obtaining and documenting informed consent is discussed in [Section 9.3](#). Please refer to the laboratory manual for instructions.

The samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for up to 20 years (where allowed by local regulations) after completion of the study research.

The site or the subject will not receive the results of mRNA analysis.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for adalimumab, AAA, infliximab, and HACA assays will be obtained at the time points as indicated in [Table 1](#).

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

The samples will be retained for no longer than 20 years after completion of the study (where allowed by local guidelines).

Collection of Samples for Adalimumab and AAA Assays

Blood samples for adalimumab and AAA assays will be collected into appropriately labeled serum collection tubes (one tube for adalimumab and one tube for AAA) without gel separator. For adalimumab assay, all samples will be obtained immediately prior to dosing at Weeks 0 (Baseline), 2, 4, 8, 12, 26, 34 and 52/Premature Discontinuation Visits and at Unscheduled Visits requiring dose change. For AAA assay, all samples will be obtained immediately prior to dosing at Weeks 0 (Baseline), 4, 8, 26 and 52/Premature Discontinuation Visits. Sufficient blood will be collected to provide approximately 1 mL serum for adalimumab assay and 1 mL serum for AAA assay.

Beginning at Week 12, for subjects who meet the criteria for disease flare, blood samples for the measurement of serum adalimumab and AAA concentrations will be collected just prior to receiving study drug at the visit requiring dose change (blinded therapy, open-label and dose-escalation).

If a subject undergoes dose de-escalation (from ew to eow dosing), blood samples will be collected for the determination of serum adalimumab and AAA concentrations, just prior to dose de-escalation. If these same subjects dose re-escalate (from eow to ew dosing) following disease flare, blood samples will be collected for the determination of serum adalimumab and AAA concentrations just prior to the dose re-escalation.

A minimum of 13 samples are planned to be collected per subject for adalimumab (8 samples) and AAA (5 samples) assays. The number of samples planned is 744 (8 samples × 93 subjects) for the adalimumab assay and 465 (5 samples × 93 subjects) for the AAA assay for the entire study.

For subjects who have a disease flare following Week 12 and require dose change (blinded therapy, escape to open-label drug, and further require dose escalation), up to 6 additional samples are planned to be collected per subject for adalimumab (3-samples) and AAA (3-samples) assays.

For subjects who enter the dose de-escalation and dose re-escalation phase, up to 4 additional samples are planned to be collected per subject for adalimumab (2-samples) and AAA (2-samples) assays.

In total, the maximum number of samples that a subject could have collected over the duration of the study would be 23 blood samples: 13 samples for the determination of adalimumab concentrations, and 10 samples for the determination of AAA concentrations.

Collection of Samples for Infliximab and HACA Assays

Blood samples for infliximab and HACA assay will be collected at Week 0 (Baseline) into appropriately labeled serum collection tubes (one tube for infliximab and one tube for HACA) without gel separator at Baseline. The sample will be obtained immediately prior to dosing. Sufficient blood will be collected to provide approximately 1 mL serum for infliximab assay and 1 mL serum for HACA assay.

The total number of samples planned will not exceed 186 (2 samples × 93 subjects) for the entire study.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab, AAA, infliximab and HACA assays will be centrifuged to separate the serum. Each serum sample will be transferred into appropriately labeled vials. Serum samples will be frozen within 2 hours after collection and will remain frozen at –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 for the handling and processing of samples will be provided from the central laboratory.

5.3.2.3 Disposition of Samples

Study sites will identify a supplier and purchase the necessary dry ice. The frozen serum samples will be packed in dry ice (pellet form) sufficient to last during transport. Samples

will be shipped pursuant to instructions from the AbbVie Monitor. An inventory of the samples included will accompany the package. Arrangements will be made with the central laboratory for the transfer of samples.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab will be determined using a validated ligand binding assay (LBA) method under the supervision of the Drug Analysis Department at AbbVie.

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

Serum concentrations of infliximab and HACA will be determined using validated assay methods under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

The following definitions are used to describe the primary and secondary variables:

Term	Definition
Clinical response per Partial Mayo Score	defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline
Clinical remission per Partial Mayo Score	defined as a PMS ≤ 2 and no individual subscore > 1
Mucosal healing	Endoscopy subscore of 0 or 1
PUCAI remission	defined as < 10
PUCAI response	defined as a decrease in PUCAI ≥ 20 points from Baseline
Clinical remission per Mayo Score	defined as a Mayo Score ≤ 2 and no individual subscore > 1
Clinical response per Mayo Score	defined as a decrease in Mayo Score ≥ 3 points and $\geq 30\%$ from Baseline
Clinical remission per 9 point Mayo Score (without SFS)	defined as a 9 point Mayo Score (without SFS) ≤ 2 and no individual subscore > 1
Clinical remission per 6 point Mayo Score (without SFS and endoscopy subscore)	defined as a 6 point Mayo Score (without SFS and endoscopy subscore) ≤ 1
Clinical remission per 9 point Mayo Score (without PGA)	defined as a 9 point Mayo Score (without PGA) ≤ 2 and no individual subscore > 1
Clinical remission per 6 point Mayo Score (without PGA and endoscopy subscore)	defined as a 6 point Mayo Score (without PGA and endoscopy subscore) ≤ 1
Clinical remission per 9 point Mayo Score (without RBS)	defined as a 9 point Mayo Score ≤ 2 (without RBS) and no individual subscore > 1
Clinical remission per 6 point Mayo Score (without RBS and endoscopy subscore)	defined as a 6 point Mayo Score (without RBS and endoscopy subscore) ≤ 1

Please refer to Section 8.1.4 for details on the sequentially rejective multiple test procedure of the dose groups used in this study versus external placebo for co-primary and ranked secondary endpoints.

5.3.3.1 Primary Variables

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1);
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore > 1).

5.3.3.2 Secondary Variables

Ranked secondary efficacy variables are:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;
4. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Additional exploratory secondary analyses will be performed for:

- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 8;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 8;

- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;
- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;
- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects in PMS response over time;
- Proportion of subjects in PMS remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points;
- Change from Baseline in hemoglobin, hematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with EIM at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy subscore of 0 or 1 (without friability) at Week 52;

- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;
- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without RBS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Change from Baseline in Mayo score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy subscore at Week 52;
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

5.3.4 Safety Variables

Vital signs, laboratory profiles, physical examinations, and adverse events will be assessed throughout the study.

5.3.5 Pharmacokinetic Variables

Pharmacokinetic

Adalimumab trough serum concentrations will be summarized by dose at each time point using descriptive statistics. In addition, pharmacokinetic model based analyses will be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity

AAA will be evaluated for each subject and each dose, and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated. HACA will be evaluated for each subject and each dose, and rates of HACA positive will be calculated.

5.3.6 Pharmacogenetic, mRNA and Serologic Variables

5.3.6.1 Pharmacogenetic Variable

Samples may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to adalimumab, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes that may be related to the disease or to drug response. Some genes that are currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may also be used for the development of diagnostic tests. The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.6.2 Cytokines, Serologic Markers and mRNA Variables

Samples may be analyzed for serologic antibodies, cytokines and mRNA profiles that may help predict disease behavior and help determine disease phenotypes or response to or tolerability of treatment. Some antibodies, immune markers or transcripts insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may also be used for the development of diagnostic tests. The results of analyses will not be reported with the study summary.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol.

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

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor (see Section 5.2 and Section 7.0).
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.

- Subject has known dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie Medical Monitor.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Termination Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. However, 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.

A final phone call will be made to the subject approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

For subjects who are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended

termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie 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, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Prior to Amendment 4, at Baseline, subjects were randomized 3:2 to one of two double-blind adalimumab induction doses (high:standard).

During the randomized double-blind induction period, subjects assigned to high dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects received adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Weeks 4 and 6. Subjects randomized to standard dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, subjects received adalimumab 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Weeks 4 and 6.

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the induction period until Week 8.

At Week 8, subjects demonstrating a clinical response per Partial Mayo Score were randomized 2:2:1 to one of two adalimumab maintenance treatment groups (standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week and matching placebo at the alternate week] or high dose [0.6 mg/kg (maximum dose of 40 mg) every week]) or to placebo, respectively.

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the maintenance period until Week 52 and re-randomization to treatment for disease flare will be done according to Amendment 3 stipulations in these subjects.

After Amendment 4, subjects will receive the open-label adalimumab high induction dose. At Week 8, subjects demonstrating a clinical response per Partial Mayo Score will be randomized 1:1 to one of two adalimumab maintenance treatment groups (standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week and matching placebo at the alternate week] or high dose [0.6 mg/kg (maximum dose of 40 mg) every week]).

Subjects will receive blinded treatment every week (ew) beginning at Week 8 and will remain on double-blinded therapy through Week 52.

Treatment of Subjects with Disease Flare During the Study

At or after Week 12:

- Subjects who are randomized to standard maintenance dose (0.6 mg/kg [maximum of 40 mg] eow) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume receiving the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
- Subjects who are randomized to high maintenance dose (0.6 mg/kg [maximum of 40 mg] ew) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume the high dose (0.6 mg/kg [maximum of 40 mg] ew).
- Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.

If a subject continues to meet the definition of disease flare (2nd time) following at least a 4-week course of blinded therapy since the subject was re-randomized for disease flare, they may be switched to open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg].

Note: If a subject was re-randomized at Week 12 (to receive either re-induction dose [2.4 mg/kg {maximum of 160 mg}] or to receive adalimumab [0.6 mg/kg {maximum of 40 mg}]), then the earliest that subject could be evaluated to determine if they meet the criteria for disease flare for switch to OL weekly dosing is at Week 16.

If a subject continues to meet the definition of disease flare (3rd time) following a 4-week course of open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab open-label 40 mg ew (maximum dose, not weight based).

Subjects with persistent disease flare while on adalimumab 40 mg ew (max dose) may be withdrawn from the study at the investigator's discretion.

During open-label rescue therapy, subjects who are responders and have been in remission for at least 8 consecutive weeks ($PMS \leq 2$ with no individual subscore > 1) may have their dosage decreased from ew to eow. The investigator should receive prior approval from the Medical Monitor before taking any action with regard to dose de-escalation.

If subjects demonstrate disease flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to adalimumab ew dosing. The investigator should receive prior approval from the Medical Monitor before taking any action with regard to dose re-escalation.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in [Table 4](#).

Table 4. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 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
Placebo	0.8 mL 0.8 mL solution for injection 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

5.5.2.1 Packaging and Labeling

All Treatment Types

Investigational product will be packaged separately in 0.8 mL vial containing either adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. Each dosing kit carton will have a unique kit ID and contains two labeled vials. Each vial and kit will be labeled per local regulatory requirements.

All labels must remain affixed to study medication at all times, and should never be removed for any reason.

Detailed instructions and training for the administration of study supplies are provided in [Appendix L](#).

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab/placebo vials are to be stored protected from light at 2°C to 8°C/36°F to 46°F. Study medication drug must not be frozen at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded every business day on a temperature log to record proper function. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study medication 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 or destroyed at the site in accordance with local regulations and per instructions from 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

All subjects will be assigned a unique identification number by the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) as they are screened for the study. Subjects who meet the selection criteria in Section 5.2.1 and Section 5.2.2 will proceed to enter the study. The randomization at Week 8 for subjects who demonstrated a clinical response per PMS will be stratified by Week 8 remission status by PMS. This treatment group assignment will be maintained by the IVRS and not provided to the site, as the subject will be referred to by the subject number assigned at screening. The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

If a subject should forget to administer the injection of study medication on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all dosing information on the Subject Diary/Dosing Log.

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned to the study site full. The subject should resume their regular dosing schedule based on the first dosing date at Baseline.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) the Investigator, study site personnel and the subject will remain blinded to each subject's treatment throughout the blinded period of the study. The IVRS/IWRS will provide access to blinded subject treatment information in the case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie Medical Monitor (see Section 7.0 prior to breaking the blind). The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)

AbbVie will establish a DMC to review the safety and key efficacy data generated during the study and to provide recommendations to AbbVie about continuing or modifying the study. The DMC will review unblinded safety data and efficacy during the study. The DMC charter will establish the frequency of meetings and suggest relevant data for review. Full details of DMC responsibilities and members and credentials will be included in the DMC Charter for Study M11-290.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study. The study drug must not be used for reasons other than that described in the protocol.

The subject or their qualified designee will administer all doses of study drug. Appropriate site staff will supervise the subject's administration of the study drug at required in-office study visits to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a subject diary/dosing log (ePRO device) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. If the subject does not bring the subject diary/dosing log to the site visit and does not return used and unused vials, IP boxes and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the subject diary/dosing log (ePRO device) is returned before completing on the applicable eCRF page.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, (in the US/Puerto Rico adequate temperature is cool to the touch, OUS US/Puerto Rico temperature recording devices [templates] are provided in the shipments) and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the site on a Site Drug Accountability log including date received, the lot number, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug.

All empty IP boxes, used and unused vials will be inventoried by the site. Each subject will be given their own sharps disposal container to store used syringes. Empty IP boxes, used and unused vials and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty boxes, used and unused vials and returned Sharps containers will be retained (unless prohibited by local law) until the CRA is onsite to confirm the returned medication. CRAs and site staff will complete study medication accountability via study medication logs, source documents, subject diary/dosing log from ePRO, viewing used and unused vials, empty IP boxes and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used vials have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the destruction methodology should be maintained at the site's facility. Unused medication will be returned by the CRA after drug accountability has been completed at the site or destroyed at the site in accordance with local regulations and per instructions from AbbVie.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

5.6.2 Appropriateness of Measurements

The design of this clinical trial was chosen to demonstrate adalimumab as an effective and safe therapy in pediatric subjects with moderately to severely active UC who failed conventional treatment. Prior to Amendment 4, at Baseline, subjects were stratified and randomized via the IVRS according to their Baseline disease severity, corticosteroid use at Baseline, and their prior exposure to anti-TNF to receive either one of the two induction

dose of adalimumab. For subjects who met the criteria for response per PMS at Week 8, the randomization was stratified by Week 8 remission status per PMS and Induction dose. After Amendment 4, subjects will receive open-label adalimumab high induction dose. At Week 8, subjects demonstrating a clinical response per PMS will be randomized 1:1 to one of two adalimumab maintenance treatment groups stratified by Week 8 remission status per PMS.

Since use of steroids and immunosuppressants are associated with significant adverse effects, subjects taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered based on the investigator's discretion starting at Week 4 and may have their immunosuppressants discontinued starting at Week 12.

Prior to Amendment 4, internal placebo was chosen as the control group during maintenance period per regulatory requirement. After Amendment 4, per agreement with the regulatory agencies, randomization to the internal placebo group will be ceased, and external placebo will be used as comparator for efficacy endpoints instead.

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The clinical efficacy measurements in this study (Mayo Score and PUCAI) are commonly used for assessing disease activity in clinical studies in subjects with UC. All clinical and laboratory procedures in this study are standard or generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with moderately to severely active UC who meet all inclusion criteria and none of the exclusion criteria are eligible for this study. The specific subject population chosen was based on unmet medical needs of currently available medical therapies as well as previous anti-TNF studies that demonstrated effectiveness in UC.

5.6.4 Selection of Doses in the Study

Doses were selected using a population pharmacokinetic model of adalimumab using data from pediatric and adult subjects with Crohn's disease (Study M06-806 and Study M02-433, respectively) and adult subjects with ulcerative colitis (Study M06-827).

Because UC disease was not a significant covariate on CL/F and V/F, and literature suggests that the demographic characteristics of pediatric subjects with CD and UC are similar, simulations were conducted using this PK model and demographic data from the pediatric CD study, Study M06-806, including age, weight, albumin concentrations and AAA rates.

The goal of the simulations was to select a standard dosing regimen that is predicted to achieve similar exposures in pediatric UC subjects compared to those exposures observed in adult UC subjects treated with a 160 mg dose at Week 0, 80 mg at Week 2, and 40 mg at Weeks 4 and 6. The high dose regimen was then selected to achieve and evaluate a higher exposure. Prior to Amendment 4, the proposed standard dosing regimen was an induction dosing regimen of 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) eow starting at Week 4. The proposed high dosing regimen was an induction regimen of 2.4 mg/kg (maximum dose of 160 mg) at Weeks 0 and 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, and 0.6 mg/kg (maximum dose of 40 mg) at Week 4.

At Week 8, subjects demonstrating a clinical response per Partial Mayo Score were randomized 2:2:1 to one of two adalimumab maintenance treatment groups (standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week and matching placebo at the alternate week] or high dose [0.6 mg/kg (maximum dose of 40 mg) every week]) or to placebo, respectively.

After Amendment 4, subjects will receive open-label adalimumab high induction dose. At Week 8, subjects demonstrating a clinical response per PMS will be randomized 1:1 to the two above mentioned adalimumab maintenance treatment groups.

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:

- Biologic compound(s)

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

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event 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 adverse event.

Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention (refer to Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
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). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

- | | |
|-----------------|---|
| Mild | The adverse event is transient and easily tolerated by the subject. |
| Moderate | The adverse event causes the subject discomfort and interrupts the subject's usual activities. |
| Severe | The adverse event causes considerable interference with the subject's 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 adverse event to the use of study drug:

- | | |
|----------------------------------|--|
| Reasonable Possibility | An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event. |
| No Reasonable Possibility | An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event. |

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

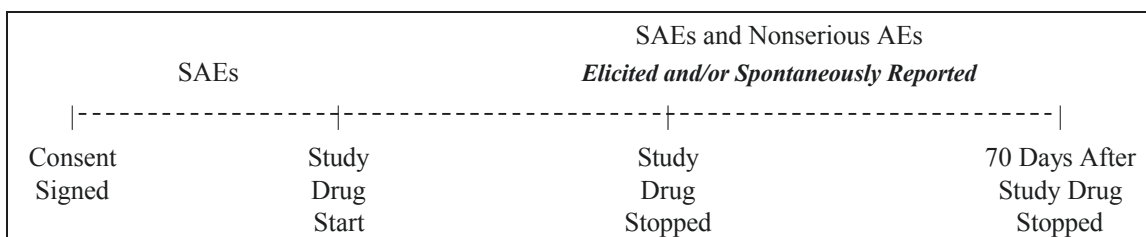
All adverse events reported from the time of study drug administration until 70 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent. Adverse event information will be collected and recorded on the appropriate eCRFs.

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs.

There may be instances where a 70-day follow-up phone call occurs after the locking of the clinical database. In this situation, any adverse events reported to AbbVie from this 70-day follow-up phone call will be evaluated for inclusion in the clinical database. All SAEs or adverse events of special interest, as defined by AbbVie, reported during the 70-day follow-up phone call must be captured in the clinical database.

Adverse event information will be collected as shown in [Figure 5](#).

Figure 5. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the physician will notify the AbbVie Clinical Pharmacovigilance within 24 hours of the physician becoming aware of the event by entering the serious adverse event or

nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the Rave system should be documented on the SAE Non-CRF forms and sent to Clinical Pharmacovigilance within 24 hours of being made aware of the adverse event by fax or email.

FAX to: [REDACTED]
[REDACTED]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
[REDACTED]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Safety Hotline: [REDACTED]
Email: [REDACTED]

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

Primary Therapeutic MD:

[REDACTED] MD
Immunology Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
[REDACTED]
Ludwigshafen 67061
Germany

Telephone Contact Information:

Phone: [REDACTED]

Fax: [REDACTED]

Cell: [REDACTED]

Email: [REDACTED]

In case of subject safety concerns or medical emergencies, should the Primary Therapeutic MD be unavailable, please call the following central back-up number:

Phone: [REDACTED]

The Sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

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 spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.0 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

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, or packaging issues.

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. 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

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Representative:

[REDACTED], MD
Immunology Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
[REDACTED]
Ludwigshafen 67061
Germany

Telephone Contact Information:

Phone: [REDACTED]

Fax: [REDACTED]

Cell: [REDACTED]

Email: [REDACTED]

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

- Subject entered into the study even though she/he 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 or prohibited 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.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in pediatric subjects with moderately to severely active ulcerative colitis. Complete, specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

8.1.1 Analyzable Population

The following populations will be used for analyses in this study:

Intent-To-Treat (ITT): The ITT population includes all subjects who received at least one dose of the study medication during induction period. ITT subjects will be analyzed as randomized/enrolled.

ITT-E: The ITT-E population will be a subpopulation of the ITT population, where subjects who have received open-label high induction dose will be excluded. ITT-E is the primary population for the induction period efficacy analyses.

Modified ITT (mITT): Consists of all Week 8 PMS Responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period. mITT is the primary population for the maintenance period efficacy analyses.

Re-Randomized population: Consists of all subjects with a disease flare who were re-randomized at or after Week 12 and received at least one dose of the study medication after the re-randomization.

Safety: Includes all subjects who received at least one dose of the study drug. The safety set will be analyzed as treated, according to treatment the subject actually received. The safety set will be used only for safety analysis.

8.1.2 Planned Methods of Statistical Analysis

Descriptive statistics will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for continuous variables; and counts and percentages for discrete variables. For confirmatory tests the multiple significance level of 0.05 will be controlled. The analysis will be performed using SAS[®] (SAS Institute Inc., Cary, NC, USA).

8.1.3 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized for each treatment group using descriptive statistics. *P* values will be provided to assess the comparability of the treatment groups assigned by randomization. Continuous variables will be analyzed using analysis of variance (ANOVA) with treatment group as factor, and discrete variables will be analyzed using Chi-square test or Fisher's exact test.

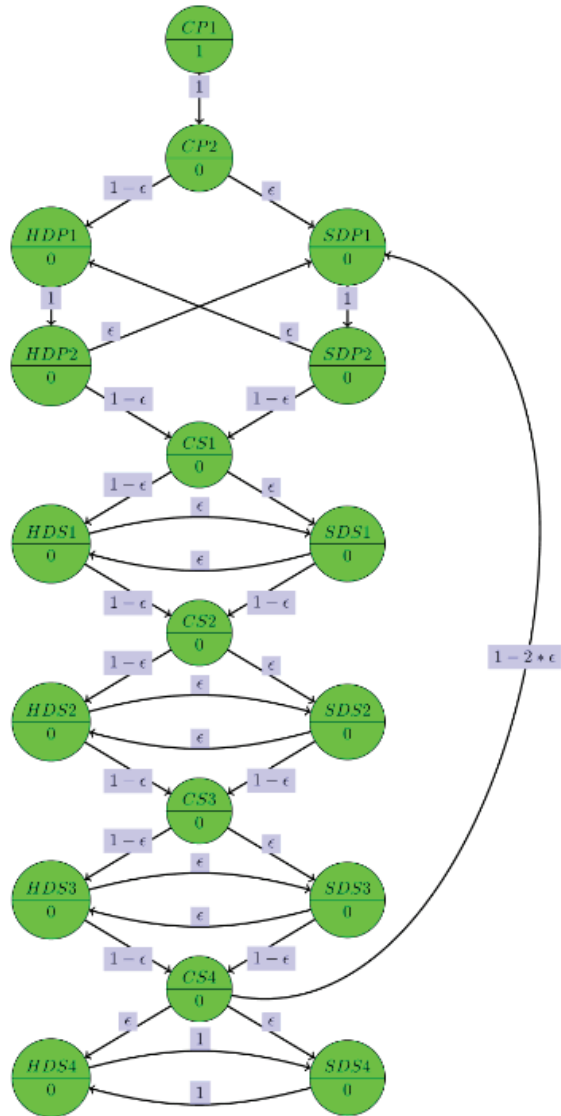
8.1.4 Statistical Analyses of Efficacy

The efficacy analysis will be performed in the ITT-E population for the Week 8 efficacy endpoints and in the mITT population for the Week 52 efficacy endpoints. Non-responder imputation (NRI) will be used to impute missing values for binary efficacy endpoints. Subjects who do not complete the induction period or who receive rescue therapy during the maintenance period will be considered as failures from that time point forward. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

8.1.4.1 Co-Primary and Ranked Secondary Efficacy Variables

Co-primary and ranked secondary endpoints will be summarized by treatment group with 95% confidence intervals (CI) and adalimumab dose groups will be tested against external placebo in a sequentially rejective multiple test procedure in order to ensure that the multiple significance level of 5% is controlled, using one sample two-sided Chi-square tests. The below graph describes the structure of the multiple test procedure that starts with testing the co-primary endpoints for the combined high and standard adalimumab dose groups versus external placebo and then individual dose groups versus external placebo separately:

Multiple Test Procedure for the Co-Primary and Ranked Secondary Endpoints



Assuming $\epsilon = 0.0005$; C = testing the endpoint for the combined high and standard adalimumab dose groups against external placebo; HD = testing the endpoint for the high adalimumab dose against external placebo; SD = testing the endpoint for the standard adalimumab dose against external placebo; P_1 = co-primary induction endpoint; P_2 = co-primary maintenance endpoint; S_i = ranked secondary endpoint i ($i = 1, \dots, 4$)

Section 8.1.4.3 contains details on assumed external placebo rates.

8.1.4.2 Additional Exploratory Secondary Efficacy Variables

Exploratory secondary endpoints that are of the binary type will be analyzed as proportions by treatment group including 95% CIs. Exploratory secondary endpoints that are of the continuous type will be analyzed as changes from baseline, and reported by treatment group including 95% CIs. Non-responder imputation (NRI) will be used to impute missing values for binary efficacy endpoints. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

The following subset of endpoints will be tested for the high adalimumab dose against the standard adalimumab dose in an exploratory manner:

- Proportion of subjects in PMS clinical remission at Week 8;
- Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;

- Proportion of subjects in PUCAI remission at Week 8;
- Proportion of subjects in PUCAI response at Week 8.

8.1.4.3 Derivation of External Placebo Control Rates

In order to derive robust external placebo assumptions for the co-primary and ranked secondary endpoints, a thorough literature search of placebo-controlled clinical studies in subjects with moderate to severe UC who had failed conventional therapy was performed. Studies M06-826 and M06-827 were the only available data sources with PMS data at Week 8. Studies GEMINI 1 and OCTAVE Sustain were the only studies with a similar subject population (i.e., failure or intolerance to prior corticosteroids or IMMs), study design (i.e., randomized withdrawal), and endpoint definitions for derivation of external placebo rates for the Week 52 endpoints in Study M11-290.

For all co-primary and ranked secondary endpoints where available, separate estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were derived as described by endpoint below. The estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were then combined as a weighted mean according to the assumed proportion of anti-TNF naïve and experienced subjects as per the Study M11-290 protocol, i.e., $0.75 \times \text{rate in anti-TNF naïve} + 0.25 \times \text{rate in anti-TNF experienced subjects}$. To be conservative, the upper limit of the 95% CI for the weighted mean was used as the external placebo assumption.

For PMS remission at Week 8: A remission rate of anti-TNF naïve placebo patients was estimated using logistic regression with anti-TNF naïve placebo patients from Studies M06-826 and M06-827 and study as a fixed effect, in order to weight the studies according to their sample sizes. Anti-TNF experienced placebo patients were only available in Study M06-827, so the remission rate from this study only was used as remission rate for anti-TNF experienced placebo patients.

For Mayo Score remission and mucosal healing at Week 52 in Week 8 responders per PMS, as well as for Mayo Score remission at Week 52 in Week 8 remitters per PMS:

Separate remission rates of anti-TNF naïve and anti-TNF experienced placebo patients were estimated using separate logistic regression models with anti-TNF naïve placebo patients and anti-TNF experienced placebo patients, respectively, from GEMINI 1 and OCTAVE Sustain and study as a fixed effect, in order to weight the studies according to their sample sizes.

For Mayo Score response Week 52 in Week 8 responders per PMS: Results were not available by anti-TNF naïve versus anti-TNF experienced placebo patients, so the overall response rates in placebo subjects from GEMINI 1 and OCTAVE Sustain were combined via logistic regression with study as a fixed effect, in order to weight the studies according to their sample sizes.

For steroid-free remission per Mayo Score at Week 52 in Week 8 responders per PMS with corticosteroids at Baseline: Only data from GEMINI 1 was available. Rates of anti-TNF naïve and anti-TNF experienced placebo patients from GEMINI 1 were combined to a weighted mean ($0.75 \times \text{rate in anti-TNF naïve} + 0.25 \times \text{rate in anti-TNF experienced subjects}$) and the upper bound of the 95% CI for the weighted mean was used.

Table 5. External Placebo Assumptions for Co-Primary and Ranked Secondary Efficacy Endpoints

Endpoint	External Placebo Rate (95% CI Upper Limit from Meta-Analysis)
Week 8 PMS Remission	19.83%
Week 52 FMS Remission in Week 8 Responders per PMS	18.37%
Week 52 FMS Response in Week 8 Responders per PMS	26.10%
Week 52 Mucosal Healing in Week 8 Responders per PMS	22.03%
Week 52 FMS Remission in Week 8 Remitters per PMS	14.79%
Week 52 FMS Remission in Week 8 Responders per PMS with CS at Baseline and Discontinuation of CS prior to Week 52	24.08%

FMS = Full Mayo Score; PMS = Partial Mayo Score; CS = Corticosteroids

8.1.5 Statistical Analyses of Safety

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed within the safety analysis set.

Treatment-emergent AEs are defined as new events that begin either on or after the first dose of the study medication and within 70 days after the last dose of the study medication.

Treatment-emergent adverse events (AEs) will be summarized by treatment group using descriptive statistics. AEs, including serious AEs, AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation (see details in the SAP), will be tabulated by system organ class and preferred term whereby the most current implemented MedDRA dictionary will be used. Also, summaries by severity and relationship to study drug will be done.

Other safety variables like laboratory data will be described by descriptive statistics as mentioned before. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

Details of this and all other analyses will be provided in the SAP.

8.1.6 Interim Analysis

No interim analyses are planned.

8.1.7 Pharmacokinetic Analyses

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by dose at each time point using descriptive statistics. In addition, pharmacokinetic model based analyses will be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

AAA will be evaluated for each subject and each dose, and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated. HACA will be evaluated for each subject and each dose, and rates of HACA positive will be calculated.

Exposure/Response:

The relationship between adalimumab concentrations and clinical response will be determined as appropriate.

8.2 Determination of Sample Size

The co-primary endpoints will be tested first for the combined high and standard adalimumab dose groups versus external placebo and then individual dose groups versus external placebo separately, controlling the multiple significance level of 5%. For each individual test the nominal power is calculated.

Assuming a 48% remission rate per PMS at Week 8 for the combined standard and high adalimumab induction dose groups and a remission rate per PMS of 19.83% for external placebo, a total of 77 subjects (high:standard = 46:31) in ITT-E population provides at least 99% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming a 36% remission rate per Mayo Score at Week 52 for the combined standard and high maintenance dose groups and a remission rate per Mayo Score of 18.37% for external placebo, a total of 57 subjects in the combined adalimumab maintenance dose groups in mITT population (e.g., high:standard = 28:29) provide 88% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming that the high adalimumab dose regimen is associated with higher efficacy than the standard adalimumab dose regimen and assuming a 52% remission rate per PMS at Week 8 for the high adalimumab induction dose group and a remission rate per PMS of

19.83% for external placebo, 46 subjects in the high adalimumab induction dose group of ITT-E population provide at least 99% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Assuming a 41% remission rate per Mayo Score at Week 52 for the high adalimumab maintenance dose groups and a remission rate per Mayo Score of 18.37% for external placebo, a total of 28 subjects in the high adalimumab maintenance dose group of the mITT population provide at least 80% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Based on the assumption of a 75% response rate at Week 8, 93 subjects will have to be included in the study (including ~12 internal placebo subjects in the maintenance part of the study who were included prior to Amendment 4) to ensure 57 subjects in the combined adalimumab maintenance dose groups.

8.3 Randomization Methods

Prior to Amendment 4, at baseline, subjects were randomized 3:2 to one of the double-blinded adalimumab induction doses (high dose or standard dose). The randomization was to be stratified by baseline disease severity (per Mayo score), prior exposure to anti-TNF, and corticosteroid use at Baseline.

At Week 8, subjects demonstrating a clinical response per Partial Mayo Score (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) were randomized in a 2:2:1 ratio to one of two adalimumab maintenance treatment groups (standard dose or high dose) or to placebo, respectively. The randomization was stratified according to Week 8 remission status per PMS and induction dose.

After Amendment 4, at Baseline, subjects will receive open-label adalimumab high induction dose.

At Week 8, subjects demonstrating a clinical response per Partial Mayo Score (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) will be randomized in a 1:1 ratio

to one of two adalimumab maintenance treatment groups (standard dose or high dose). The randomization will be stratified according to Week 8 remission status per PMS.

At or after Week 12, subjects with a disease flare may be re-randomized to receive the blinded-treatments as shown in [Figure 4](#).

The randomization schedule will be prepared by the Statistics Department of AbbVie.

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. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. 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. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events 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. 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 study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in [Appendix A](#).

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and the subject's parent/legal guardian, and answer all questions regarding this study. Pediatric subjects will be included in all discussions in order to obtain verbal or written assent. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IRB requirements, an informed assent form may also be obtained by each subject prior to any study-related procedures being performed. If a subject becomes of legal age during the course of the study, that subject will need to be re-consented.

A copy of the informed consent form and the assent form will be given to the subject and the subject's parent/legal guardian and the original 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.

Genetic and non-genetic biomarker analysis will only be performed if the subject's parent/legal guardian has voluntarily signed and dated a separate genetic and non-genetic biomarker informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject and subject's parent/legal guardian has had an opportunity to ask questions. The separate genetic and non-genetic biomarker informed consent must be signed before the genetic and non-genetic biomarker testing is performed. If the

subject's parent/legal guardian does not consent to the genetic and non-genetic biomarker testing, it will not impact the subject's participation in the study.

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 following assessments that will be completed by the subject and/or subject's parent/legal guardian or physician will be considered source documentation:

- IMPACT III
- WPAI: UC – Caregiver

The adverse event electronic data capture case report form (eCRF) data segments of: alternate etiology, severity, frequency and relationship to study drug, may also be used as source and will require an Investigator approval on the eCRF as verification of the accuracy of the information.

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.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being

collected with an electronic data capture (EDC) system called Rave[®] provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system, except for subject-completed questionnaires, which will be completed on paper by the subject then transcribed into the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Patient Reported Outcomes (PRO) data is collected directly onto paper CRFs by the subjects. The completion of these forms is verified by the site staff. The forms are

entered into the clinical database and then can be viewed within the EDC system by the site staff.

All questionnaires must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, the date of the correction, the reason for the correction, and the initials of the person making the correction. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry.

10.3 Electronic Patient Reported Outcomes (ePRO)

Subject reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) tool called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO tool is available through the vendor, CRF Health, while the user acceptance testing of the study-specific ePRO design will be conducted and maintained at AbbVie.

The subject will be entering the data into an electronic device, these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the trial. This access will be available for the duration of the trial to the investigational sites, as well as delegated personnel. Such access will be removed from investigational sites following the receipt of the study archive. Data from the ePRO tool will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigational site at that time as a durable record of the site's ePRO data. It will be possible for the investigational site to create paper printouts from that media.

The ePRO data (such as stool frequency, rectal bleeding, abdominal discomfort, and general well-being) will be collected electronically via a handheld device into which the

subject will record the required pieces of information on a daily basis. In addition, study drug administration data (such as kit number, vial number and amount administered) will be collected electronically via a handheld device into which the subject will record this required information on a weekly basis. The electronic device will be programmed to allow data entry for throughout the day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff, will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

10.4 Data Collection Process

AbbVie is using an Electronic Patient Reported Outcome (ePRO) tool to capture portions of the clinical data defined in this protocol. The use of ePRO requires certain process changes compared to the use of traditional paper PROs. Trial-Specific Guidelines (T-SGs) have been developed to document the changes from the traditional paper PRO process. These T-SGs govern the ePRO processes in this trial.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 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 governmental 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 trial-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.

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or subject management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by

both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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 (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
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.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis

Protocol Date: 20 November 2018

Signature of Principal Investigator _____
Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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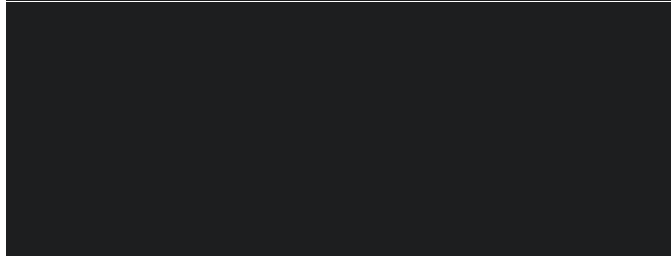
Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees [e.g., independent ethics committee (IEC) or institutional review board (IRB)] review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
		Statistics
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Appendix C. Pediatric Ulcerative Colitis Activity Index (PUCAI)

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in < 50% of stools	10
Small amount with most stools	20
Large amount (> 50% of stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
> 8	15
5. Nocturnal stools (any episode causing waking)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
TOTAL MAXIMUM SCORE	85

The Pediatric Ulcerative Colitis Activity Index (PUCAI) is the copyright of The Hospital for Sick Children, Toronto, Canada, authored by Dr. Anne Griffiths, Dr. Dan Turner and Dr. Anthony Otley. The PUCAI will be provided under license from The Hospital for Sick Children and must not be copied, distributed or used in any way without the prior written consent of The Hospital for Sick Children.

Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology*. 2007;133:423-432.

Appendix D. Mayo Scoring System

The Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopic appearance subscore, and Physician's Global Assessment subscore.

<p>Stool Frequency Subscore*</p> <p>0 = Normal</p> <p>1 = 1 – 2 stools/day more than normal</p> <p>2 = 3 – 4 stools/day more than normal</p> <p>3 = > 4 stools/day more than normal</p> <p>* Each subject serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.</p>
<p>Rectal Bleeding Subscore**</p> <p>0 = None</p> <p>1 = Visible blood with stool less than half the time</p> <p>2 = Visible blood with stool half of the time or more</p> <p>3 = Passing blood alone</p> <p>**A score of 3 for bleeding requires subjects to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.</p>
<p>Endoscopy Subscore:</p> <p>0 = Normal or inactive disease</p> <p>1 = Mild disease (erythema, decreased vascular pattern, mild friability)</p> <p>2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)</p> <p>3 = Severe disease (spontaneous bleeding, ulceration)</p>
<p>Physician's Global Assessment Subscore***</p> <p>0 = Normal</p> <p>1 = Mild disease</p> <p>2 = Moderate disease</p> <p>3 = Severe disease</p> <p>*** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.</p>

Adapted from Schroeder et al., and from Lewis et al.^{21,22}

Script for Collection of Mayo Scores

The Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore.

The Partial Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, and Physician's Global Assessment subscore.

Stool Frequency Subscore

The stool frequency subscore is calculated by comparing the stool frequency to a normal number of bowel movements. The normal number of bowel movements is the number of stools per day (24 hours) that is typical for the subject when having active UC but not experiencing a flare and needs to be designated once prior to enrollment. The normal number of bowel movements should represent a full number of at least 1.

Subjects will record the daily number of stools throughout the trial. Using these numbers, the Stool Frequency subscore will be assessed for each study day as follows:

- A number of bowel movements lower than or equal to the normal number of bowel movements should be scored as 0 = Normal.
- One or 2 bowel movements more than the normal number of bowel movements should be scored as 1.
- Three or 4 bowel movements more than the normal number of bowel movements should be scored as 2.
- Five or more bowel movements more than the normal number of bowel movements should be scored as 3.

The Stool Frequency subscores from the 5 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit. In order to account for unavailable or excluded diary entries as per the provisions given below diary entries of the most recent 5 days within 14 days prior to each study visit will be used.

The Stool Frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3. Diary entries for stool frequency should not be included in the 5 days prior to the visit that are evaluated for the Stool Frequency subscore for the following days: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the

endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 5 days prior to the respective study visit.

Rectal Bleeding Subscore

Subjects should record a daily rectal bleeding subscore value as follows:

- No visible blood with stool during the respective day should be scored as 0.
- Visible blood with stool less than half the time during the respective day should be scored as 1.
- Visible blood with stool at least half the time during the respective day should be scored as 2.
- A score of 3 for bleeding requires subjects to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

The score entries into subject's diary from the 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit. In order to account for unavailable or excluded diary entries as per the provisions given below diary entries of the most recent 5 days within 14 days prior to each study visit will be used.

Diary entries for rectal bleeding should not be included in the 5 days prior to the visit that are evaluated for the Rectal Bleeding subscore for the following days: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 5 days prior to the respective study visit.

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the 2 subject-reported subscores, the endoscopy subscore as applicable, the subject's daily record of abdominal discomfort and functional assessment during the 5 days prior to the visit, and other observations such as

physical findings, and the subject's performance status in order to assess disease activity as follows:

- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

Endoscopy Subscore

The endoscopist should evaluate each observed segment of the colon (rectum, sigmoid, descending colon, transverse colon, ascending colon/cecum) by using the classification as follows:

- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

The endoscopic subscore for the subject will be the worst score of the observed segments.

The local endoscopist should also separately assess presence or absence of friability (yes/no).

The endoscopy will be recorded on a video tape and will undergo a central review process for endoscopy subscore assessment.

Appendix E. Loss of Response and Intolerance to Anti-TNF Agent

To enroll in this study, subjects who have previously been exposed to an anti-TNF agent, including infliximab, must meet one of the two conditions defined below.

Loss of Response

The investigator judges the subject to have responded to the anti-TNF agent in the past and demonstrated a loss of response after a full and adequate course of anti-TNF therapy based on the investigator's assessment.

Intolerance to Anti-TNF Agent

A subject is defined as intolerant when, in the opinion of the investigator, therapy was discontinued as a result of a significant acute or delayed reaction to the medication.

**Appendix F. Work Productivity and Activity Impairment Questionnaire:
Ulcerative Colitis V2.0 (WPAI: UC) – Caregiver**

The following questions ask about the effect of your child's ulcerative colitis 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 7 days, how many hours did you miss from work because of problems associated with your child's ulcerative colitis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your child's ulcerative colitis. Do not include time you missed for your child to participate in this study.*

_____ HOURS

3. During the past 7 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 7 days, how much did your child's ulcerative colitis 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 ulcerative colitis affected your work only a little, choose a low number. Choose a high number if your child's ulcerative colitis affected your work a great deal.

Consider only how much your child's ulcerative colitis affected productivity while you were working.

My child's Ulcerative colitis had no effect on my work	_____										My child's Ulcerative colitis completely prevented me from working	
	0	1	2	3	4	5	6	7	8	9	10	
	CIRCLE A NUMBER											

6. During the past seven days, how much did your child's ulcerative colitis 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 ulcerative colitis affected your activities only a little, choose a low number. Choose a high number if your child's ulcerative colitis affected your activities a great deal.

Consider only how much your child's ulcerative colitis affected your ability to do your regular daily activities, other than work at a job.

My child's Ulcerative colitis had no effect on my daily activities

0 1 2 3 4 5 6 7 8 9 10

My child's Ulcerative colitis completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:UC – Caregiver V2.0 (US English)

Appendix G. Study Drug Packaging and Administration

Prior to Amendment 4

During the Double-Blind Induction Period

Week	Standard Induction Dose	High Induction Dose
0 (Baseline)	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>
1	Matching PBO <i>Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>
2	Blinded study drug adalimumab 1.2 mg/kg Maximum dose of 80 mg <i>Maximum amount to administer is 1.6 mL</i>	Blinded study drug adalimumab 1.2 mg/kg Maximum dose of 80 mg <i>Maximum amount to administer is 1.6 mL</i>
4	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>
6	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>

During the Maintenance Period

Week	PBO	Standard Maintenance Dose	High Maintenance Dose
8 – 50 i.e., Wks 8, 10, 12, 14, 16, 18 to Wk 50)	Matching PBO <i>Maximum amount to administer is 0.8 mL</i>	Blinded Study Drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>	Blinded Study Drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>
9 – 51 i.e., Wks 9, 11, 13, 15, 17, 19 ... to Wk 51	Matching PBO <i>Maximum amount to administer is 0.8 mL</i>	Matching PBO <i>Maximum amount to administer is 0.8 mL</i>	Blinded Study Drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>

Disease Flare During Maintenance Period

Week	PBO		Standard Maintenance Dose		High Maintenance Dose	
	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)
Disease Flare						
Re-Induction Dose (1 st time) At or after Week 12	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Plus</i> Matching Placebo <i>Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Plus</i> Matching Placebo <i>Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Plus</i> Matching Placebo <i>Maximum amount to administer is 3.2 mL</i>

Disease Flare During Maintenance Period (Continued)

Week	PBO		Standard Maintenance Dose		High Maintenance Dose	
	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)
One week after Re-Induction dose	If subject receives Re-Induction dose at site on Even week (i.e., Wk 22, 24, 26, ...), then subject must start with <u>vial 2</u> at home at the week after Re-Induction dose.		If subject receives Re-Induction dose at site on Even week (i.e., Wk 22, 24, 26, ...), then subject must start with <u>vial 2</u> at home at the week after Re-Induction dose.		If subject receives Re-Induction dose at site on Even week (i.e., Wk 22, 24, 26, ...), then subject must start with <u>vial 2</u> at home at the week after Re-Induction dose.	
	Matching PBO <i>Maximum amount to administer is 0.8 mL</i>		Matching PBO <i>Maximum amount to administer is 0.8 mL</i>		Blinded study drug adalimumab 0.6 mg/kg <i>Maximum dose of 40 mg</i> <i>Maximum amount to administer is 0.8 mL</i>	
	The following weeks, subject will use vial 1, then vial 2, continue like this until next site visit.		The following weeks, subject will use vial 1, then vial 2, continue like this until next site visit.		The following weeks, subject will use vial 1, then vial 2, continue like this until next site visit.	

Disease Flare During Maintenance Period (Continued)

Week	PBO		Standard Maintenance Dose		High Maintenance Dose	
	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)
One week after Re-Induction dose (continued)	If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with <u>vial 1</u> at home at the week after Re-Induction dose.	If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with <u>vial 1</u> at home at the week after Re-Induction dose.	If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with <u>vial 1</u> at home at the week after Re-Induction dose.	If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with <u>vial 1</u> at home at the week after Re-Induction dose.	If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with <u>vial 1</u> at home at the week after Re-Induction dose.	If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with <u>vial 1</u> at home at the week after Re-Induction dose.
	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.

Disease Flare During Maintenance Period (Continued)

Escape to Open-Label Drug (Weight Based)

Disease Flare adalimumab 0.6 mg/kg
2nd Time (at least Maximum dose of 40 mg
 after 4 weeks of *Maximum amount to administer is 0.8 mL*
 re-induction dose) Administered every week

Dose Escalation (MAX DOSE – NOT Weight Based)

Disease Flare Adalimumab 40 mg/0.8 mL
3rd Time (after at Adalimumab 40 mg
 least 4 weeks on *Amount to administer is 0.8 mL*
 open-label standard Administered every week
 dose)

Dose De-Escalation and Dose Re-Escalation During Maintenance Period

Dose De-Escalation	Open-label study drug adalimumab 40 mg/0.8 mL Administered every other week
Dose Re-Escalation	Open-label study drug adalimumab 40 mg/0.8 mL Administered every week

After Amendment 4

During the Open-Label Induction Period

Week	High Induction Dose
0 (Baseline)	Open-label study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>
1	Open-label study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>
2	Open-label study drug adalimumab 1.2 mg/kg Maximum dose of 80 mg <i>Maximum amount to administer is 1.6 mL</i>
4	Open-label study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>
6	Open-label study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>

During the Maintenance Period

Week	Standard Maintenance Dose	High Maintenance Dose
8 – 50 i.e., Wks 8, 10, 12, 14, 16, 18 to Wk 50)	Blinded Study Drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>	Blinded Study Drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>
9 – 51 i.e., Wks 9, 11, 13, 15, 17, 19... to Wk 51	Matching PBO <i>Maximum amount to administer is 0.8 mL</i>	Blinded Study Drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i>

Disease Flare During Maintenance Period

Week	Standard Maintenance Dose		High Maintenance Dose	
	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)
Disease Flare				
Re-Induction Dose (1 st time) At or after Week 12	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Plus Matching Placebo Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 2.4 mg/kg Maximum dose of 160 mg <i>Maximum amount to administer is 3.2 mL</i>	Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Plus Matching Placebo Maximum amount to administer is 3.2 mL</i>
One week after Re-Induction dose	If subject receives Re-Induction dose at site on Even week (i.e., Wk 22, 24, 26, ...), then subject must start with <u>vial 2</u> at home at the week after Re-Induction dose. Matching PBO <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 1, then vial 2, continue like this until next site visit.		If subject receives Re-Induction dose at site on Even week (i.e., Wk 22, 24, 26, ...), then subject must start with <u>vial 2</u> at home at the week after Re-Induction dose. Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> The following weeks, subject will use vial 1, then vial 2, continue like this until next site visit.	

Disease Flare During Maintenance Period (Continued)

Week	Standard Maintenance Dose		High Maintenance Dose	
	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)	Re-Induction Dose of 2.4 mg/kg (max 160 mg)	Dose 0.6 mg/kg (max 40 mg)
Disease Flare				
One week after Re-Induction dose (continued)	<p>If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with vial 1 at home at the week after Re-Induction dose.</p> <p>Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i></p> <p>The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.</p>		<p>If subject receives Re-Induction dose at site on Odd week (i.e., Wk 21, 23, 25, ...), then subject must start with vial 1 at home at the week after Re-Induction dose.</p> <p>Blinded study drug adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i></p> <p>The following weeks, subject will use vial 2, then vial 1, continue like this until next site visit.</p>	

Escape to Open-Label Drug (Weight Based)

Disease Flare 2nd Time (at least after 4 weeks of re-induction dose)	adalimumab 0.6 mg/kg Maximum dose of 40 mg <i>Maximum amount to administer is 0.8 mL</i> Administered every week
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Dose Escalation (MAX DOSE – NOT Weight Based)

Disease Flare 3rd Time (after at least 4 weeks on open-label standard dose)	Adalimumab 40 mg/0.8 mL Adalimumab 40 mg <i>Amount to administer is 0.8 mL</i> Administered every week
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Dose De-Escalation and Dose Re-Escalation During Maintenance Period

Dose De-Escalation	Open-label study drug adalimumab 40 mg/0.8 mL Administered every other week
Dose Re-Escalation	Open-label study drug adalimumab 40 mg/0.8 mL Administered every week

Appendix H. Body Weight Adjusted Volumes of Study Drug for Administration of Induction and Maintenance Doses

Part 1. Body Weight Adjusted Volumes of Study Drug for Administration of Induction Dose at BL and Week 1

Weight (Kg)	Administered (# of vial used)	Kit 1		Kit 2		Administered (# of vial used)	Weight (Kg)	Kit 1		Kit 2		Administered (# of vial used)	Weight (Kg)	Kit 1		Kit 2	
		Vial 1	Vial 2	Vial 1	Vial 2			Vial 1	Vial 2	Vial 1	Vial 2			Vial 1	Vial 2		
14	1 x	0.67	NA	NA	NA	4 x	36	0.43	0.43	0.43	0.43	4 x	58	0.70	0.70	0.70	0.70
15	1 x	0.72	NA	NA	NA	4 x	37	0.44	0.44	0.44	0.44	4 x	59	0.71	0.71	0.71	0.71
16	1 x	0.77	NA	NA	NA	4 x	38	0.46	0.46	0.46	0.46	4 x	60	0.72	0.72	0.72	0.72
17	2 x	0.41	0.41	NA	NA	4 x	39	0.47	0.47	0.47	0.47	4 x	61	0.73	0.73	0.73	0.73
18	2 x	0.43	0.43	NA	NA	4 x	40	0.48	0.48	0.48	0.48	4 x	62	0.74	0.74	0.74	0.74
19	2 x	0.46	0.46	NA	NA	4 x	41	0.49	0.49	0.49	0.49	4 x	63	0.76	0.76	0.76	0.76
20	2 x	0.48	0.48	NA	NA	4 x	42	0.50	0.50	0.50	0.50	4 x	64	0.77	0.77	0.77	0.77
21	2 x	0.50	0.50	NA	NA	4 x	43	0.52	0.52	0.52	0.52	4 x	65	0.78	0.78	0.78	0.78
22	2 x	0.53	0.53	NA	NA	4 x	44	0.53	0.53	0.53	0.53	4 x	66	0.79	0.79	0.79	0.79
23	2 x	0.55	0.55	NA	NA	4 x	45	0.54	0.54	0.54	0.54	4 x	67	0.80	0.80	0.80	0.80
24	2 x	0.58	0.58	NA	NA	4 x	46	0.55	0.55	0.55	0.55	4 x	68	0.80	0.80	0.80	0.80
25	2 x	0.60	0.60	NA	NA	4 x	47	0.56	0.56	0.56	0.56	4 x	69	0.80	0.80	0.80	0.80
26	2 x	0.62	0.62	NA	NA	4 x	48	0.58	0.58	0.58	0.58	4 x	70	0.80	0.80	0.80	0.80
27	2 x	0.65	0.65	NA	NA	4 x	49	0.59	0.59	0.59	0.59	4 x	71	0.80	0.80	0.80	0.80
28	2 x	0.67	0.67	NA	NA	4 x	50	0.60	0.60	0.60	0.60	4 x	72	0.80	0.80	0.80	0.80
29	2 x	0.70	0.70	NA	NA	4 x	51	0.61	0.61	0.61	0.61	4 x	73	0.80	0.80	0.80	0.80
30	2 x	0.72	0.72	NA	NA	4 x	52	0.62	0.62	0.62	0.62	4 x	74	0.80	0.80	0.80	0.80
31	2 x	0.74	0.74	NA	NA	4 x	53	0.64	0.64	0.64	0.64	4 x	75	0.80	0.80	0.80	0.80

Weight (Kg)	Administered (# of vial used)		Kit 1 Vial 1		Kit 2 Vial 1		Weight (Kg)		Administered (# of vial used)		Kit 1 Vial 1		Kit 2 Vial 1		Weight (Kg)		Administered (# of vial used)		Kit 1 Vial 1		Kit 2 Vial 1	
	Kit 1 Vial 1	Kit 2 Vial 1	Kit 1 Vial 2	Kit 2 Vial 2	Kit 1 Vial 1	Kit 2 Vial 1	Kit 1 Vial 2	Kit 2 Vial 2	Kit 1 Vial 1	Kit 2 Vial 1	Kit 1 Vial 2	Kit 2 Vial 2	Kit 1 Vial 1	Kit 2 Vial 1	Kit 1 Vial 2	Kit 2 Vial 2	Kit 1 Vial 1	Kit 2 Vial 1	Kit 1 Vial 2	Kit 2 Vial 1	Kit 1 Vial 2	Kit 2 Vial 2
32	0.77	NA	0.77	NA	0.65	NA	54	4 x	0.65	0.65	0.65	0.65	0.80	0.80	76	4 x	0.80	0.80	0.80	0.80	0.80	0.80
33	0.79	NA	0.79	NA	0.66	NA	55	4 x	0.66	0.66	0.66	0.66	0.80	0.80	77	4 x	0.80	0.80	0.80	0.80	0.80	0.80
34	0.41	0.41	0.41	0.41	0.67	0.41	56	4 x	0.67	0.67	0.67	0.67	0.80	0.80	78	4 x	0.80	0.80	0.80	0.80	0.80	0.80
35	0.42	0.42	0.42	0.42	0.68	0.42	57	4 x	0.68	0.68	0.68	0.68	0.80	0.80	79	4 x	0.80	0.80	0.80	0.80	0.80	0.80
															80	4 x	0.80	0.80	0.80	0.80	0.80	0.80

Part 2. Body Weight Adjusted Volumes of Study Drug for Administration of Induction Dose at Week 2

Weight (Kg)	Administered (# of vial used)		Kit 1 Vial 1		Kit 1 Vial 2		Weight (Kg)		Administered (# of vial used)		Kit 1 Vial 1		Kit 1 Vial 2	
	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2	Kit 1 Vial 1	Kit 1 Vial 2	Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2	Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2	
14	1 x	0.34	NA	0.44	0.44	37	2 x	0.44	0.44	60	2 x	0.72	0.72	
15	1 x	0.36	NA	0.46	0.46	38	2 x	0.46	0.46	61	2 x	0.73	0.73	
16	1 x	0.38	NA	0.47	0.47	39	2 x	0.47	0.47	62	2 x	0.74	0.74	
17	1 x	0.41	NA	0.48	0.48	40	2 x	0.48	0.48	63	2 x	0.76	0.76	
18	1 x	0.43	NA	0.49	0.49	41	2 x	0.49	0.49	64	2 x	0.77	0.77	
19	1 x	0.46	NA	0.50	0.50	42	2 x	0.50	0.50	65	2 x	0.78	0.78	
20	1 x	0.48	NA	0.52	0.52	43	2 x	0.52	0.52	66	2 x	0.79	0.79	
21	1 x	0.50	NA	0.53	0.53	44	2 x	0.53	0.53	67	2 x	0.80	0.80	
22	1 x	0.53	NA	0.54	0.54	45	2 x	0.54	0.54	68	2 x	0.80	0.80	
23	1 x	0.55	NA	0.55	0.55	46	2 x	0.55	0.55	69	2 x	0.80	0.80	
24	1 x	0.58	NA	0.56	0.56	47	2 x	0.56	0.56	70	2 x	0.80	0.80	
25	1 x	0.60	NA	0.58	0.58	48	2 x	0.58	0.58	71	2 x	0.80	0.80	

Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2	Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2	Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2	Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1	Kit 1 Vial 2
26	1 x	0.62	NA	49	2 x	0.59	0.59	72	2 x	0.80	0.80	72	2 x	0.80	0.80
27	1 x	0.65	NA	50	2 x	0.60	0.60	73	2 x	0.80	0.80	73	2 x	0.80	0.80
28	1 x	0.67	NA	51	2 x	0.61	0.61	74	2 x	0.80	0.80	74	2 x	0.80	0.80
29	1 x	0.70	NA	52	2 x	0.62	0.62	75	2 x	0.80	0.80	75	2 x	0.80	0.80
30	1 x	0.72	NA	53	2 x	0.64	0.64	76	2 x	0.80	0.80	76	2 x	0.80	0.80
31	1 x	0.74	NA	54	2 x	0.65	0.65	77	2 x	0.80	0.80	77	2 x	0.80	0.80
32	1 x	0.77	NA	55	2 x	0.66	0.66	78	2 x	0.80	0.80	78	2 x	0.80	0.80
33	1 x	0.79	NA	56	2 x	0.67	0.67	79	2 x	0.80	0.80	79	2 x	0.80	0.80
34	2 x	0.41	0.41	57	2 x	0.68	0.68	80	2 x	0.80	0.80	80	2 x	0.80	0.80
35	2 x	0.42	0.42	58	2 x	0.70	0.70								
36	2 x	0.43	0.43	59	2 x	0.71	0.71								

Part 3. Body Weight Adjusted Volumes of Study Drug for Administration of Induction Dose at Week 4 and 6

Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)	Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)	Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)
14	1 x	0.17	0.17	36	1 x	0.43	0.43	58	1 x	0.70	0.70
15	1 x	0.18	0.18	37	1 x	0.44	0.44	59	1 x	0.71	0.71
16	1 x	0.19	0.19	38	1 x	0.46	0.46	60	1 x	0.72	0.72
17	1 x	0.20	0.20	39	1 x	0.47	0.47	61	1 x	0.73	0.73



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Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)	Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)	Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)	Weight (Kg)	Administered (# of vial used)	Week 4 Kit 1 Vial 1 Volume (ml)	Week 6 Kit 1 Vial 2 Volume (ml)
18	1 x	0.22	0.22	40	1 x	0.48	0.48	62	1 x	0.74	0.74	62	1 x	0.74	0.74
19	1 x	0.23	0.23	41	1 x	0.49	0.49	63	1 x	0.76	0.76	63	1 x	0.76	0.76
20	1 x	0.24	0.24	42	1 x	0.50	0.50	64	1 x	0.77	0.77	64	1 x	0.77	0.77
21	1 x	0.25	0.25	43	1 x	0.52	0.52	65	1 x	0.78	0.78	65	1 x	0.78	0.78
22	1 x	0.26	0.26	44	1 x	0.53	0.53	66	1 x	0.79	0.79	66	1 x	0.79	0.79
23	1 x	0.28	0.28	45	1 x	0.54	0.54	67	1 x	0.80	0.80	67	1 x	0.80	0.80
24	1 x	0.29	0.29	46	1 x	0.55	0.55	68	1 x	0.80	0.80	68	1 x	0.80	0.80
25	1 x	0.30	0.30	47	1 x	0.56	0.56	69	1 x	0.80	0.80	69	1 x	0.80	0.80
26	1 x	0.31	0.31	48	1 x	0.58	0.58	70	1 x	0.80	0.80	70	1 x	0.80	0.80
27	1 x	0.32	0.32	49	1 x	0.59	0.59	71	1 x	0.80	0.80	71	1 x	0.80	0.80
28	1 x	0.34	0.34	50	1 x	0.60	0.60	72	1 x	0.80	0.80	72	1 x	0.80	0.80
29	1 x	0.35	0.35	51	1 x	0.61	0.61	73	1 x	0.80	0.80	73	1 x	0.80	0.80
30	1 x	0.36	0.36	52	1 x	0.62	0.62	74	1 x	0.80	0.80	74	1 x	0.80	0.80
31	1 x	0.37	0.37	53	1 x	0.64	0.64	75	1 x	0.80	0.80	75	1 x	0.80	0.80
32	1 x	0.38	0.38	54	1 x	0.65	0.65	76	1 x	0.80	0.80	76	1 x	0.80	0.80
33	1 x	0.40	0.40	55	1 x	0.66	0.66	77	1 x	0.80	0.80	77	1 x	0.80	0.80
34	1 x	0.41	0.41	56	1 x	0.67	0.67	78	1 x	0.80	0.80	78	1 x	0.80	0.80
35	1 x	0.42	0.42	57	1 x	0.68	0.68	79	1 x	0.80	0.80	79	1 x	0.80	0.80
				80	1 x			80	1 x			80	1 x		

Part 4. Body Weight Adjusted Volumes of Study Drug for Administration of Maintenance Dose Starting at Week 8 to Week 51

Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)
14	1 x	0.17	36	1 x	0.43	58	1 x	0.70			
15	1 x	0.18	37	1 x	0.44	59	1 x	0.71			
16	1 x	0.19	38	1 x	0.46	60	1 x	0.72			
17	1 x	0.20	39	1 x	0.47	61	1 x	0.73			
18	1 x	0.22	40	1 x	0.48	62	1 x	0.74			
19	1 x	0.23	41	1 x	0.49	63	1 x	0.76			
20	1 x	0.24	42	1 x	0.50	64	1 x	0.77			
21	1 x	0.25	43	1 x	0.52	65	1 x	0.78			
22	1 x	0.26	44	1 x	0.53	66	1 x	0.79			
23	1 x	0.28	45	1 x	0.54	67	1 x	0.80			
24	1 x	0.29	46	1 x	0.55	68	1 x	0.80			
25	1 x	0.30	47	1 x	0.56	69	1 x	0.80			
26	1 x	0.31	48	1 x	0.58	70	1 x	0.80			
27	1 x	0.32	49	1 x	0.59	71	1 x	0.80			
28	1 x	0.34	50	1 x	0.60	72	1 x	0.80			
29	1 x	0.35	51	1 x	0.61	73	1 x	0.80			
30	1 x	0.36	52	1 x	0.62	74	1 x	0.80			
31	1 x	0.37	53	1 x	0.64	75	1 x	0.80			



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Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)
32	1 x	0.38	54	1 x	0.65	76	1 x	0.80			
33	1 x	0.40	55	1 x	0.66	77	1 x	0.80			
34	1 x	0.41	56	1 x	0.67	78	1 x	0.80			
35	1 x	0.42	57	1 x	0.68	79	1 x	0.80			
						80	1 x	0.80			

Appendix I. Body Weight Adjusted Volumes of Study Drug for Administration of Dose After Re-Randomization for Disease Flare

Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1 Volume (ml)	Kit 1 Vial 2 Volume (ml)	Kit 2 Vial 1 Volume (ml)	Kit 2 Vial 2 Volume (ml)
14	4 x	0.17	0.17	0.17	0.17
15	4 x	0.18	0.18	0.18	0.18
16	4 x	0.19	0.19	0.19	0.19
17	4 x	0.20	0.20	0.20	0.20
18	4 x	0.22	0.22	0.22	0.22
19	4 x	0.23	0.23	0.23	0.23
20	4 x	0.24	0.24	0.24	0.24
21	4 x	0.25	0.25	0.25	0.25
22	4 x	0.26	0.26	0.26	0.26
23	4 x	0.28	0.28	0.28	0.28
24	4 x	0.29	0.29	0.29	0.29
25	4 x	0.30	0.30	0.30	0.30
26	4 x	0.31	0.31	0.31	0.31
27	4 x	0.32	0.32	0.32	0.32
28	4 x	0.34	0.34	0.34	0.34
29	4 x	0.35	0.35	0.35	0.35
30	4 x	0.36	0.36	0.36	0.36
31	4 x	0.37	0.37	0.37	0.37
32	4 x	0.38	0.38	0.38	0.38
33	4 x	0.40	0.40	0.40	0.40
34	4 x	0.41	0.41	0.41	0.41
35	4 x	0.42	0.42	0.42	0.42
36	4 x	0.43	0.43	0.43	0.43
37	4 x	0.44	0.44	0.44	0.44
38	4 x	0.46	0.46	0.46	0.46
39	4 x	0.47	0.47	0.47	0.47
40	4 x	0.48	0.48	0.48	0.48
41	4 x	0.49	0.49	0.49	0.49
42	4 x	0.50	0.50	0.50	0.50

Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1 Volume (ml)	Kit 1 Vial 2 Volume (ml)	Kit 2 Vial 1 Volume (ml)	Kit 2 Vial 2 Volume (ml)
43	4 x	0.52	0.52	0.52	0.52
44	4 x	0.53	0.53	0.53	0.53
45	4 x	0.54	0.54	0.54	0.54
46	4 x	0.55	0.55	0.55	0.55
47	4 x	0.56	0.56	0.56	0.56
48	4 x	0.58	0.58	0.58	0.58
49	4 x	0.59	0.59	0.59	0.59
50	4 x	0.60	0.60	0.60	0.60
51	4 x	0.61	0.61	0.61	0.61
52	4 x	0.62	0.62	0.62	0.62
53	4 x	0.64	0.64	0.64	0.64
54	4 x	0.65	0.65	0.65	0.65
55	4 x	0.66	0.66	0.66	0.66
56	4 x	0.67	0.67	0.67	0.67
57	4 x	0.68	0.68	0.68	0.68
58	4 x	0.70	0.70	0.70	0.70
59	4 x	0.71	0.71	0.71	0.71
60	4 x	0.72	0.72	0.72	0.72
61	4 x	0.73	0.73	0.73	0.73
62	4 x	0.74	0.74	0.74	0.74
63	4 x	0.76	0.76	0.76	0.76
64	4 x	0.77	0.77	0.77	0.77
65	4 x	0.78	0.78	0.78	0.78
66	4 x	0.79	0.79	0.79	0.79
67	4 x	0.80	0.80	0.80	0.80
68	4 x	0.80	0.80	0.80	0.80
69	4 x	0.80	0.80	0.80	0.80
70	4 x	0.80	0.80	0.80	0.80
71	4 x	0.80	0.80	0.80	0.80
72	4 x	0.80	0.80	0.80	0.80
73	4 x	0.80	0.80	0.80	0.80
74	4 x	0.80	0.80	0.80	0.80

Weight (Kg)	Administered (# of vial used)	Kit 1 Vial 1 Volume (ml)	Kit 1 Vial 2 Volume (ml)	Kit 2 Vial 1 Volume (ml)	Kit 2 Vial 2 Volume (ml)
75	4 x	0.80	0.80	0.80	0.80
76	4 x	0.80	0.80	0.80	0.80
77	4 x	0.80	0.80	0.80	0.80
78	4 x	0.80	0.80	0.80	0.80
79	4 x	0.80	0.80	0.80	0.80
80	4 x	0.80	0.80	0.80	0.80

Appendix J. Body Weight Adjusted Volumes of Study Drug for Administration of OL Adalimumab 0.6 mg/kg Dosing (weight based)

Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)	Weight (Kg)	Administered (# of vial used)	Volume (ml)
14	1 x	0.17	36	1 x	0.43	58	1 x	0.70
15	1 x	0.18	37	1 x	0.44	59	1 x	0.71
16	1 x	0.19	38	1 x	0.46	60	1 x	0.72
17	1 x	0.20	39	1 x	0.47	61	1 x	0.73
18	1 x	0.22	40	1 x	0.48	62	1 x	0.74
19	1 x	0.23	41	1 x	0.49	63	1 x	0.76
20	1 x	0.24	42	1 x	0.50	64	1 x	0.77
21	1 x	0.25	43	1 x	0.52	65	1 x	0.78
22	1 x	0.26	44	1 x	0.53	66	1 x	0.79
23	1 x	0.28	45	1 x	0.54	67	1 x	0.80
24	1 x	0.29	46	1 x	0.55	68	1 x	0.80
25	1 x	0.30	47	1 x	0.56	69	1 x	0.80
26	1 x	0.31	48	1 x	0.58	70	1 x	0.80
27	1 x	0.32	49	1 x	0.59	71	1 x	0.80
28	1 x	0.34	50	1 x	0.60	72	1 x	0.80
29	1 x	0.35	51	1 x	0.61	73	1 x	0.80
30	1 x	0.36	52	1 x	0.62	74	1 x	0.80
31	1 x	0.37	53	1 x	0.64	75	1 x	0.80
32	1 x	0.38	54	1 x	0.65	76	1 x	0.80
33	1 x	0.40	55	1 x	0.66	77	1 x	0.80
34	1 x	0.41	56	1 x	0.67	78	1 x	0.80
35	1 x	0.42	57	1 x	0.68	79	1 x	0.80
						80	1 x	0.80



Appendix K. 70-Day Follow-Up Call – Sample

Site Name/Number: _____

Subject Number: _____

Please contact subjects who discontinue adalimumab 70 days following study 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 three attempts.)
- 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. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.)

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

If events are listed above, your monitor will review and retrieve the appropriate eCRF pages during their next visit.

Appendix L. Injection Instructions – Sample Vial

Subject Instructions

0.8 mL dose

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Tables of Contents

Dosing Schedule

General Information and Supplies

Injection Procedures

Study Drug Dosing Schedule

Subject Number: _____

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

The injection for the visits at Baseline, Weeks 1, 2, 4, 8, 12, 18, 26, 34, 42 and 52 will be done during your visit at the doctor's office. After Week 4, on weeks between office visits (i.e., Weeks 6, 9, 10, 11, 13, etc.) study drug will be self-administered at home by you or someone trained to give you the injections.

The study drug should be administered on the same day of the week for each dose.

Starting at Week 8, study drug will be administered once a week by you or someone trained to give you the injections.

The vials in the kits will be numbered 1 and 2. You MUST use the vials in order.

At each visit, site personnel will measure your weight and inform you the volume of study drug that you will be taken (milliliter [ml] or cc). You must use the suggested volume up until your site personnel provide you with the new volume of study drug to be taken.

Please return all used and unused vials, the Sharps container and empty boxes 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 suggested dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject diary/dosing log.

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

General Information

- Vials will be labeled "Adalimumab" versus Placebo.
- Store all adalimumab vials in your refrigerator NOT in the freezer. Should the medication accidentally become frozen, call your study doctor's office.
- Study medication 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 AND NEW SYRINGE EVERY INJECTION DAY. There may be medication left in the vial. DO NOT RE-USE.
- Save all study medications. ***All vials (used and unused) and empty boxes 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** _____ or proceed to your nearest emergency room.

Injection Procedures (Vials)

1. Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one kit with the vial(s) of adalimumab from the refrigerator. Do not use a vial that has been frozen or if it has been left in direct sunlight.
- Return any unused vial(s) to the refrigerator.

You will need the following items for each dose:

- study medication

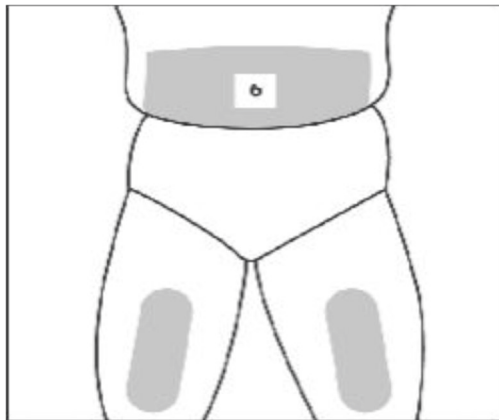
- sterile capped syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

- Make sure the liquid in the vial is clear and colorless. Do not use if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special Sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

2. Choosing and preparing an injection site

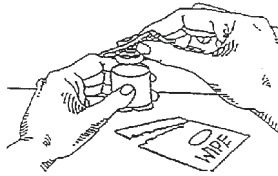


- Wash your hands well.
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).

- Choose a different site each time you give yourself an injection. Each new injection should be given at least 1 inch from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.

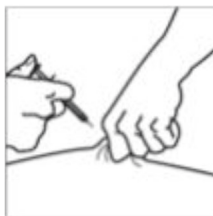
3. How to prepare your adalimumab dose for injection with a vial

- Remove the plastic cap from the vial.
- Wipe the gray stopper with an alcohol swab and discard alcohol swab.



- Place the vial upright on a hard, flat surface.
- 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.)
- 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.")*
- Push the plunger in, forcing air into the vial.

- 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.)*
- Adjust the volume in the syringe to the quantity advised by your physician.
- With the needle still in the vial, check the syringe for air bubbles. To remove any air bubbles, start by gently tapping the syringe.
- 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.)
- Withdraw the needle from the vial, being careful not to touch it to any surface.
- Take the syringe in one hand.
- Hold the syringe upright with the needle facing down.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay.
- Do not shake the syringe.



4. Injecting Adalimumab

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly.
- You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.

- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject adalimumab. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. Do not use the same syringe. Dispose of it in your special Sharps container. If no blood appears, slowly push the plunger all the way in until all of the adalimumab is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- After injection, immediately apply a single finger stroke to the Activation-Assist™ lever arm to activate the shielding mechanism.



- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your Sharps container.

Appendix M. Non-Drug Materials Provided to the Study Sites

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

Tote Bags

Coolers

Gel Packs

Subject Diaries

Sharps Containers

Appendix N. The Measurements and Volume(s) of Blood Samples to Be Drawn

The measurements and volume(s) of blood samples to be drawn at the time point indicated in the table below:

Visit	Measurement	Volume (mL)	Total Blood Volume (mL)/ Visit
Screen	Chemistry, hCG [#]	2.5	12.5
	Hepatitis Serology	2.5	
	ANA/dsDNA	2.5	
	Hematology	2.0	
	QuantiFERON TB Gold**	3.0	
Baseline	Chemistry, hCG*, hsCRP	2.5	21.0
	Hematology	2.0	
	Infliximab and HACA	4.0	
	Adalimumab	2.0	
	AAA	2.0	
	Serologic Markers and Cytokines***	4.0	
	mRNA***	2.5	
	PG***	2.0	
Week 1	hCG*	2.5	2.5
Week 2	Chemistry, hCG*, hsCRP	2.5	6.5
	Hematology	2.0	
	Adalimumab	2.0	
Week 4	Chemistry, hCG*, hsCRP	2.5	8.5
	Hematology	2.0	
	Adalimumab	2.0	
	AAA	2.0	
Week 8	Chemistry, hCG*, hsCRP	2.5	15.0
	Hematology	2.0	
	Adalimumab	2.0	
	AAA	2.0	
	Serologic Markers and Cytokines***	4.0	
	mRNA***	2.5	

Visit	Measurement	Volume (mL)	Total Blood Volume (mL)/ Visit
Week 12	Chemistry, hCG*, hsCRP	2.5	6.5
	Hematology	2.0	
	Adalimumab	2.0	
Week 18	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 26	Chemistry, hCG*, hsCRP	2.5	15.0
	Hematology	2.0	
	Adalimumab	2.0	
	AAA	2.0	
	Serologic Markers and Cytokines***	4.0	
	mRNA***	2.5	
Week 34	Chemistry, hCG*, hsCRP	2.5	6.5
	Hematology	2.0	
	Adalimumab	2.0	
Week 42	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 52/Premature Discontinuation	Chemistry, hCG, [#] hsCRP	2.5	18.0
	Hematology	2.0	
	Adalimumab	2.0	
	AAA	2.0	
	Serologic Markers and Cytokines***	4.0	
	mRNA***	2.5	
	QuantiFERON TB Gold [^]	3.0	
Total			121

Only performed in female of childbearing potential.

* Only performed in female of childbearing potential that has positive urine pregnancy test.

** Subjects will not have the QuantiFERON test performed, if a PPD test is used or in case of a negative test within 90 days prior to Screening, provided nothing has changed in the subject's medical history.

*** Samples will only be collected for subjects who signed the separate informed consent.

[^] For subjects with a negative TB test at Screening, TB test will be required at Week 52. An annual TB screen testing will not be required for subjects who have been treated for latent or active TB or have had a positive TB test at any time (prior to the study, at Screening, or testing performed at any time point during the study).

Appendix O. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis

Previously read:

AbbVie Inc.	Protocol Number: M11-290
Name of Study Drug: Adalimumab	Phase of Development: 3
Name of Active Ingredient: Adalimumab	Date of Protocol Synopsis: 02 November 2017
Protocol Title: A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis	
Objective: The objective of the study is to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously (SC) in pediatric subjects with moderate to severe ulcerative colitis (UC).	
Investigators: Multicenter	
Study Sites: Approximately 50 sites worldwide for the main study and approximately 10 sites for the Japan sub-study.	
Study Population: Subjects with moderate-to-severe UC from the ages of 4 to 17 prior to Baseline dosing.	
Number of Subjects to be Enrolled: Approximately 85 subjects for the main study and up to approximately 20 subjects for the Japan sub-study	
Methodology: This is a Phase 3, multicenter, randomized, double-blind trial designed to evaluate the efficacy and safety of adalimumab in pediatric subjects with moderate to severe ulcerative colitis, who have failed therapy with corticosteroids and/or immunosuppressants.	

Methodology (Continued):

Approximately 85 pediatric subjects for the main study (and up to approximately 20 subjects for the Japan sub-study) with moderate-to-severe UC (Mayo Score of 6 to 12 points with an endoscopy subscore of 2 to 3, confirmed by central reader) will be enrolled at approximately 50 sites worldwide (and approximately 10 sites for the Japan sub-study). The study will allow enrollment of up to 25% of anti-TNF experienced subjects. Prior to Amendment 4, subjects who met all of the inclusion criteria and none of the exclusion criteria were to be enrolled and randomized 3:2 at Baseline to one of two double-blinded adalimumab induction doses (high dose or standard dose). The randomization was to be stratified by baseline disease severity (per Mayo score), prior exposure to anti-TNF, and corticosteroid use at Baseline. During the randomized double-blind induction period, subjects assigned to high induction dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects received adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Subjects randomized to the standard induction dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, adalimumab 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. After Amendment 4, subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and receive open-label adalimumab high induction dose. During the open-label induction period, subjects will receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects will receive adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6.

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the induction period until Week 8.

Prior to Amendment 4, at Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) were randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) and Induction dose in a 2:2:1 ratio to one of two adalimumab maintenance treatment groups (Standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or High dose [0.6 mg/kg (maximum dose of 40 mg) every week]) or to placebo, respectively.

After Amendment 4, at Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) will be randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) in a 1:1 ratio to one of two adalimumab maintenance treatment groups (Standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or High dose [0.6 mg/kg (maximum dose of 40 mg) every week]).

Subjects will receive blinded treatment every week (ew) beginning at Week 8 and will remain on double-blinded therapy through Week 52.

- Subjects who are randomized to standard dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) every other week (eow) and will receive the matching placebo at the alternate week.
- Subjects who are randomized to high dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) ew.
- Subjects who were randomized to placebo prior to Amendment 4 receive matching placebo ew.

Methodology (Continued):

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the maintenance period until Week 52 and re-randomization to treatment for disease flare will be done according to Amendment 3 stipulations in these subjects.

At Week 8, subjects who have not achieved a clinical response per PMS will be discontinued. A safety evaluation call will be made 70 days after the last dose of study drug is administered to obtain follow-up information on any ongoing or new adverse events.

The duration of the study could be up to 66 weeks, which includes a Screening Period of up to 28 days, 8-week induction period and a 44-week double-blind maintenance period and a 70-day follow-up. Upon completion of the study, subjects will have the option to enroll into an open-label extension study where they will receive open-label adalimumab.

Treatment of Subjects with Disease Flare During the Study:

Criteria for Disease Flare are as follows:

- Subjects with a Week 8 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Week 8 score.

Subjects will be expected to remain on blinded therapy throughout the 44-week maintenance period.

However, subjects with a disease flare, may be re-randomized to receive the following blinded-treatment at or after Week 12:

- Subjects who are randomized to Standard maintenance dose (0.6 mg/kg [maximum dose of 40 mg] eow) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume receiving the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
- Subjects who are randomized to High maintenance dose (0.6 mg/kg [maximum dose of 40 mg] ew) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew).
- Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.

If a subject continues to meet the definition of disease flare (2nd time) following at least a 4-week course of blinded therapy since the subject has been re-randomized for disease flare, they may be switched to open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg]. *If a subject was re-randomized at Week 12 (to receive either re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]), then the earliest that subject could be evaluated to determine if the subject meets the criteria for disease flare for switch to OL (0.6 mg/kg [maximum of 40 mg]) weekly dosing is at Week 16.*

Methodology (Continued):

Treatment of Subjects with Disease Flare During the Study (Continued):

If a subject continues to meet the definition of disease flare (3rd time) following a 4-week course of open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab open-label 40 mg ew (maximum dose, not weight-based).

Subjects with persistent disease flare while on adalimumab 40 mg ew (max dose) may be withdrawn from the study at the investigator's discretion.

During open-label rescue therapy, subjects who are responders and have been in remission for at least 8 consecutive weeks ($PMS \leq 2$ with no individual subscore > 1) may have their dosage decreased from ew to eow. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose de-escalation.

If subjects demonstrate disease flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to adalimumab ew dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose re-escalation.

For subjects who meet the criteria for dose change, blood samples (adalimumab, AAA and hs-CRP) will be collected just prior to receiving any dose change (blinded therapy, escape to open-label adalimumab, dose de-escalation and dose re-escalation).

Subjects are allowed to be treated with stable doses of UC-related concomitant medications during the study, with the following exceptions and requirements:

- At or after Week 4, subjects taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered based on the investigator's discretion. A proposed tapering schedule is specified in Section 5.3.1.1.
- From Week 4 to Week 12, if the subject should experience an increase in symptoms after corticosteroid was tapered, the subject may have their corticosteroid dose increased back up to the corticosteroid dose at Baseline. This increase must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Subjects who experience disease flare at or after Week 12 are allowed to change their dose or initiate treatment with corticosteroids, immunosuppressant or 5-ASA; these increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.
- Immunosuppressant therapy may be discontinued at or after Week 12 at the investigator's discretion.

At each study visit, in addition to routine physical examination including evaluation of extra intestinal manifestations and calculation of the PMS and PUCAI, the following will be collected:

- Anthropometric evaluations at Baseline, Week 26 and Week 52/Premature Discontinuation for determination of body mass index (BMI), and "z" scores for height and weight.
- IMPACT III Quality of Life questionnaire at Baseline, Week 8, Week 26 and Week 52/Premature Discontinuation Visit will be completed for subjects 9 years or older at the Baseline study visit.
- Bone age determination by x-ray of the wrist at Screening and at Week 52/Premature Discontinuation Visit in subjects who have not completed linear growth.
- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26 Week 34 and Week 52/Premature Discontinuation Visit and at Unscheduled Visit requiring dose change.

Methodology (Continued):

Treatment of Subjects with Disease Flare During the Study (Continued):

- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 8, Week 26 and Week 52/Premature Discontinuation Visit and at Unscheduled Visit requiring dose change.
- Tanner stage at Baseline, Week 26 and Week 52/Premature Discontinuation Visit.
- Endoscopy subscore at Screening and Week 52/Premature Discontinuation Visit.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subjects from the ages of 4 to 17 prior to baseline dosing.
2. Subjects with a diagnosis of UC for at least 12 weeks prior to screening confirmed by endoscopy with biopsy.

A colonoscopy will be performed during the screening period unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis without evidence of dysplasia, colon cancer or infection). In this case the screening endoscopy may be either a colonoscopy or a flexible sigmoidoscopy.

If the subject underwent an endoscopy within 56 days of Baseline, and a video recording of the endoscopy is available, the video recording may be used and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met and all technical requirements are fulfilled.

Note:

- If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must also be performed.
 - Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.
3. Active ulcerative colitis with a Mayo Score of 6 – 12 points and endoscopy subscore of 2 – 3 (confirmed by central reader) despite concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):
 - Oral prednisone of ≥ 2 mg/day or equivalent, but not exceeding 40 mg/day, or oral budesonide ≥ 3 mg/day, but not exceeding 9 mg/day, with a stable dose for at least 7 days prior to Baseline; and/or
 - At least a consecutive 28-day course of azathioprine or 6-MP or methotrexate (MTX) prior to Baseline, with a stable dose prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of 230 – 450 pmol/ 8×10^8 RBC on the current dosing regimen or MTX ≥ 15 mg/m² body surface area/week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Note: If subjects are on both oral corticosteroid and immunosuppressants BOTH of the drugs need to meet the above criteria; and/or

- Concurrent therapy with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) is not required for subjects who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

4. Parent or guardian has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed or before any concomitant medication is discontinued for the purpose of this study. Pediatric subjects will be included in all discussions in order to obtain verbal and/or written assent.
5. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
6. Subject has a negative TB Screening Assessment.
If a subject has a positive (≥ 5 mm induration) PPD test and/or IGRA test at Screening, a CXR (PA and lateral view) must be performed for evaluation of active TB disease. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.
7. If female, subject who is either not of childbearing potential, defined as pre-menstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.
Examples of approved methods of birth control include the following (see local informed consent for more detail):
 - Total abstinence from sexual intercourse;
 - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
 - Hormonal contraceptives for 90 days prior to study drug administration;
 - A vasectomized partner.
8. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

Main Exclusion:

1. Subject with Crohn's disease (CD) or indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subjects with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Therapeutic enema or suppository within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of colectomy or subtotal colectomy (with ostomy) or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil, within 30 days prior to Baseline.
7. Female subjects who are breast-feeding or considering becoming pregnant during the study.
8. Positive pregnancy test at Screening or Baseline.
9. History of clinically significant drug or alcohol abuse in the last 12 months.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

10. Subjects on azathioprine or 6-mercaptopurine (6-MP) or MTX and subjects:
 - Have not been on stable doses of these medications for at least 28 days prior to Baseline; or
 - Have discontinued these medications within 28 days of Baseline.
11. Subjects on oral aminosalicylates who:
 - Have not been on stable doses of these medications for at least 14 days prior to Baseline; or
 - Have discontinued use of aminosalicylates within 14 days of Baseline.
12. Subjects on growth hormone who have not been on a stable dose for at least 4 weeks prior to Baseline.
13. Subjects on oral corticosteroids who:
 - Have not been on stable doses of these drugs for at least 7 days prior to Baseline; or
 - Discontinued use of oral corticosteroid within 14 days of Baseline; or
 - Have been taking both budesonide and prednisone (or equivalent) simultaneously.
14. Received intravenous corticosteroids within 5 days prior to Screening or during the Screening Period.
15. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.
16. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.
17. Previous treatment with adalimumab or previous participation in an adalimumab clinical study.
18. Positive *Clostridium difficile* (*C. difficile*) stool assay during the Screening Period.
19. Currently receiving total parenteral nutrition (TPN).
20. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
21. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).
22. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
23. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
24. Subject with a positive result for the Hepatitis B surface antigen (HBs Ag) or any HBV DNA PCR result that meets or exceeds detection sensitivity will be excluded.
25. Chronic recurring infections or active TB.
26. Subject has been treated with any investigational drug of chemical or biologic nature or any investigational procedure (including previous fecal transplantation) within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline Visit.
27. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
28. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab (Tysabri[®]) or efalizumab (Raptiva[®]) or rituximab (Rituxan[®]).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

29. Known hypersensitivity to adalimumab or its excipients.
30. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

If the Screening endoscopy shows evidence of dysplasia or malignancy, subject may not be enrolled in the study.

31. Screening laboratory and other analyses show any of the following abnormal results:
 - ECG – with clinically significant abnormalities;
 - Aspartate transaminases (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range;
 - Total bilirubin ≥ 3 mg/dL;
 - Serum creatinine > 1.6 mg/dL;
 - Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Product:	Adalimumab
Induction Dose:	<p>Body weight adjusted induction dose regimen</p> <p>Prior to Amendment 4 subjects were randomized to receive one of 2 double-blind adalimumab induction doses.</p> <p><u>Standard Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and matching placebo at Week 1. Subjects received 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects received a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p> <p><u>High Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and Week 1. Subjects received 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects received a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p> <p>After Amendment 4 subjects will receive the open-label adalimumab high induction dose.</p> <p><u>High Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and Week 1. Subjects will receive 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects will receive a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p>

Double-Blind Maintenance Doses (in Week 8 PMS Responders only):	<p>Body weight adjusted maintenance dose regimen</p> <p><u>Blinded adalimumab Standard dosing regimen:</u> 0.6 mg/kg (maximum dose of 40 mg) eow with matching placebo at the alternate week</p> <p><u>Blinded adalimumab High dosing regimen:</u> 0.6 mg/kg (maximum dose of 40 mg) ew</p> <p>Subjects who were randomized to placebo (prior to Amendment 4) receive placebo ew.</p> <p>At or after Week 12 subjects who demonstrate a disease flare may be re-randomized to receive the following blinded-treatment.</p> <ul style="list-style-type: none"> • Subjects, who are randomized to standard maintenance dose, will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume to receiving the standard dose adalimumab (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule. • Subjects who are randomized to high maintenance dose, will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume to receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew). • Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
Open-Label Maintenance Doses:	<p>High dose body weight adjusted.</p> <p>0.6 mg/kg (maximum dose of 40 mg) ew</p> <p>If a subject continues to meet the definition of disease flare following a 4-week course of open-label adalimumab ew at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab 40 mg ew (maximum dose, not weight-based).</p>
Mode of Administration:	<p>Subcutaneous injection (SC)</p>
Reference Therapy:	<p>NA (after Amendment 4); Placebo (prior to Amendment 4)</p>
Dose:	<p>NA</p>
Mode of Administration:	<p>NA (after Amendment 4); Subcutaneous injection (SC) (prior to Amendment 4)</p>

Duration of Treatment: 52 weeks

- The subjects will visit the site at Screening, Baseline, Weeks 1, 2, 4, 8, 12, 18, 26, 34, 42, and 52/Premature Discontinuation and Unscheduled Visits.
- Subjects who qualify will be given the opportunity to enroll into an open-label study of the Long-term Safety and Tolerability of Repeated Administration of Adalimumab.

A 70-Day Follow-Up phone call will be completed for all subjects who either terminate early from the study or do not rollover into the extension study.

Criteria for Evaluation:

Efficacy analysis will be based on the Intent-To-Treat (ITT) population for the induction period and modified ITT (mITT) population for the maintenance period. The ITT population consists of all randomized subjects who received at least one SC injection of the study medication. Subjects who receive open-label high induction dose will be excluded from the ITT population. The mITT population consists of all Week 8 PMS Responders who were randomized at Week 8 and received at least one SC injection of the study medication during maintenance period.

The safety analysis set will include all subjects who received at least one SC injection of the study medication.

Efficacy:

This study will utilize the Mayo Score, PMS and Mayo subscores to measure efficacy. The PUCAI will also be utilized as applicable.

Primary Efficacy Endpoints

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1) in the high induction dose group as compared to external placebo.
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore > 1) in the high maintenance dose group as compared to external placebo.

External placebo rates will be identified from an ongoing meta-analysis of relevant publically available clinical trials.

Ranked secondary efficacy endpoints are:

1. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS (high maintenance dose versus external placebo);
2. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS (high maintenance dose versus external placebo) (*);
3. Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
4. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo);
5. Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);

Criteria for Evaluation (Continued):

Efficacy (Continued):

6. Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
7. Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
8. Proportion of subjects in Partial Mayo clinical remission at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo);
9. Proportion of subjects in Partial Mayo clinical remission at Week 8 (standard induction dose versus external placebo);
10. Proportion of subjects in Mayo clinical remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo);
11. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore in Week 8 responders per PMS (standard maintenance dose versus external placebo);
12. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS (standard maintenance dose versus external placebo) (*);
13. Proportion of subjects in PUCAI remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
14. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo);
15. Proportion of subjects in PUCAI response at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
16. Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
17. Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
18. Proportion of subjects in Partial Mayo clinical remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo).

(*): If external placebo data are not available, results will only be summarized by maintenance dose group and 95% confidence intervals (CI) will be provided.

Additional secondary endpoints are the following:

- Proportion of subjects in Partial Mayo clinical remission at Week 8 (high induction dose versus standard induction dose);
- Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in Mayo clinical response at Week 52 (high maintenance dose versus standard maintenance dose);

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Proportion of subjects in Mayo clinical remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in Partial Mayo clinical remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in PUCAI remission at Week 8 (high induction dose versus standard induction dose);
- Proportion of subjects in PUCAI response at Week 8 (high induction dose versus standard induction dose);
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;
- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;
- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects in Partial Mayo response over time;
- Proportion of subjects in Partial Mayo remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points;
- Change from Baseline in hemoglobin, hematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with extraintestinal manifestations (EM) at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy subscore of 0 or 1 (without friability) at Week 52;
- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
- Proportion of subjects in a 9 point Mayo (without RBS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8 (high induction dose versus external placebo) (*);
- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8 (high induction dose versus external placebo) (*);
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8 (high induction dose versus external placebo) (*);
- Change from Baseline in Mayo score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy subscore at Week 52;
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

(*). If external placebo data are not available, results will only be summarized in the high maintenance or high induction dose group, respectively, and 95% CI will be provided.

Pharmacokinetic:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline, Weeks 2, 4, 8, 12, 26, 34 and 52/Premature Discontinuation Visits, and at Unscheduled Visits requiring dose change. Blood samples will be collected for the measurement of serum anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Weeks 4, 8, 26 and 52/Premature Discontinuation Visits and at Unscheduled Visits requiring dose change. Blood samples will be collected for the measurement of serum Influximab and HACA at Baseline (prior to dosing).

Safety:

Adverse events, laboratory data, and vital signs will be assessed at all visits throughout the study.

Statistical Methods:

Efficacy:

The efficacy analysis will be performed in the ITT set for the induction period and in the mITT set for the maintenance period. NRI method will be used to impute missing values for binary efficacy endpoints. Subjects who do not complete the induction period or who receive rescue therapy during the maintenance period will be considered as failures from that time point forward. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

The primary efficacy analysis for the co-primary endpoint at Week 8 is based on external placebo comparison identified from an ongoing meta-analysis of relevant publically available clinical trials. In order to demonstrate efficacy of adalimumab at Week 8 in the pediatric population, the lower limit of the 95% CI for the remission rate per PMS in the high induction dose group is required to be higher than the upper limit of the 95% CI of the remission rate of external placebo (assumptions based on the adult UC Studies M06-826 and M06-827 are shown in the following table for illustrative purposes only).

The primary efficacy analysis for the co-primary endpoint at Week 52 is based on the comparison of the high maintenance dose group versus external placebo using the same efficacy criterion described above.

Placebo Data from Adult UC Studies

Endpoint	Placebo Subjects by Prior Anti-TNF Status			
	Experienced n/N (%)	Naïve n/N (%)	Weighted Average for 25% Experienced +75% Naïve	
			%	95% CI Upper Limit
Week 8 Partial Mayo Score Remission (Pooled Studies M06-826 and M06-827 IAS-E set ^a)	15/101 (14.9%)	61/367 (16.6%)	16.18%	19.52%
Week 52 Mayo Score Remission (Study M06-827 ITT set)	3/101 (3.0%)	18/145 (12.4%)	10.05%	13.81%

a. IAS-E data set consisted of all randomized subjects with confirmed UC who received at least 1 dose of blinded study drug in either Study M06-826 or Study M06-827.

Secondary endpoints that are of the binary type will be analyzed using 95% confidence intervals. Comparisons to external placebo will be done as described above. Secondary endpoints that are of the continuous type will be analyzed as changes from baseline, and reported for the two treatment groups including 95% confidence intervals.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics. In addition, pharmacokinetic model based analyses will be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Statistical Methods (Continued):

Immunogenicity:

AAA will be evaluated for each subject and each regimen, and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated. HACA will be evaluated for each subject and each regimen, and rates of HACA positive will be calculated.

Safety:

Treatment-emergent Adverse Events (AEs) and serious adverse events (SAEs) will be summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. A summary of AEs by severity and relationship to study drug will be performed. Changes in laboratory and vital sign data will be summarized using descriptive statistics. Shift tables will be provided.

Sample Size:

The Week 8 co-primary endpoint is to compare the lower limit of the 95% CI of the remission rate per PMS in the adalimumab high induction dose group in this study to the upper limit of the 95% CI of the corresponding external placebo rate to be identified from a meta-analysis of relevant publically available clinical trials. For illustrative purposes only, the following calculations use results from adult UC studies (Studies M06-826 and M06-827) as an estimate for the external placebo rates. Assuming a 48.33% remission rate per PMS at Week 8 for the high induction dose group and given an upper limit of the 95% CI for the remission rate per PMS of the external placebo of 19.52%, a sample size of 65 subjects (high:standard = 39:26) provides at least 97% power for a one sample two-sided Chi-square test using a significance level of 5% for the Week 8 co-primary endpoint.

The Week 52 co-primary endpoint is to compare the lower limit of the 95% CI of the remission rate per Mayo score in the adalimumab high maintenance dose group in this study to the upper limit of the 95% CI of the external placebo rate. Assuming a 36.63% remission rate per Mayo score at Week 52 for the high maintenance dose group and given an upper limit of the 95% CI for the remission rate per Mayo score of the external placebo of 13.81%, a sample size of 54 subjects (high:standard = 27:27) in the maintenance period of the study provides at least 85% power for a one sample two-sided Chi-square test using a significance level of 5% for the Week 52 co-primary endpoint.

Based on the assumption of a 75% response rate at Week 8, a total of 85 subjects are needed in the study (including internal placebo subjects enrolled prior to Amendment 4).

Statistical Methods (Continued):

Sample Size (Continued):

Sample Size Based on Week 8 and Week 52 Co-Primary Endpoints

Endpoints	External Placebo upper 95% CI	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Induction Phase Sample Size
Week 8 PMS Remission Rate	19.52% ^a	48.33%	97%	39	Induction High:Standard 3:2 = 39:26	85 ^{b,c}
Endpoints	External Placebo Upper 95% CI	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Maintenance Phase Sample Size
Week 52 FMS Remission Rate	13.81% ^a	36.63%	85%	27	Maintenance High:Standard 1:1 = 27:27	63 ^{b,d}

PMS = partial Mayo score; FMS = full Mayo score

- The upper limit of 95% CI for placebo derived from adult UC Studies M06-826 and M06-827 for illustrative purposes only in the absence of results from the ongoing meta-analysis.
- Sample size calculation is based on a one group Chi-square test.
- 85 subjects are needed assuming 75% PMS response rate at Week 8.
- Including subjects enrolled into the internal placebo arm (prior to Amendment 4).

Has been changed to read:

AbbVie Inc.	Protocol Number: M11-290
Name of Study Drug: Adalimumab	Phase of Development: 3
Name of Active Ingredient: Adalimumab	Date of Protocol Synopsis: 20 November 2018
Protocol Title: A Multicenter, Randomized, Double-Blind Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis	
Objective: The objective of the study is to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously (SC) in pediatric subjects with moderate to severe ulcerative colitis (UC).	
Investigators: Multicenter	
Study Sites: Approximately 50 sites worldwide for the main study and approximately 10 sites for the Japan sub-study.	
Study Population: Subjects with moderate-to-severe UC from the ages of 4 to 17 prior to Baseline dosing.	
Number of Subjects to be Enrolled: 93 subjects for the main study and up to approximately 9 subjects for the Japan sub-study	
Methodology: This is a Phase 3, multicenter, randomized, double-blind trial designed to evaluate the efficacy and safety of adalimumab in pediatric subjects with moderate to severe ulcerative colitis, who have failed therapy with corticosteroids and/or immunosuppressants.	

Methodology (Continued):

93 pediatric subjects for the main study (and up to approximately 9 subjects for the Japan sub-study) with moderate-to-severe UC (Mayo Score of 6 to 12 points with an endoscopy subscore of 2 to 3, confirmed by central reader) will be enrolled at approximately 50 sites worldwide (and approximately 10 sites for the Japan sub-study). The study will allow enrollment of up to 25% of anti-TNF experienced subjects. Prior to Amendment 4, subjects who met all of the inclusion criteria and none of the exclusion criteria were to be enrolled and randomized 3:2 at Baseline to one of two double-blinded adalimumab induction doses (high dose or standard dose). The randomization was to be stratified by baseline disease severity (per Mayo Score), prior exposure to anti-TNF, and corticosteroid use at Baseline. During the randomized double-blind induction period, subjects assigned to high induction dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects received adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Subjects randomized to the standard induction dose group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, adalimumab 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. After Amendment 4, subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and receive open-label adalimumab high induction dose. During the open-label induction period, subjects will receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1. At Week 2, subjects will receive adalimumab 1.2 mg/kg (maximum dose of 80 mg), followed by a dose of 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the induction period until Week 8.

Prior to Amendment 4, at Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) were randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) and Induction dose in a 2:2:1 ratio to one of two adalimumab maintenance treatment groups (Standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or High dose [0.6 mg/kg (maximum dose of 40 mg) every week]) or to placebo, respectively.

After Amendment 4, at Week 8, subjects demonstrating a clinical response per PMS (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) will be randomized and stratified by Week 8 remission status per PMS (defined as a PMS ≤ 2 and no individual subscore > 1) in a 1:1 ratio to one of two adalimumab maintenance treatment groups (Standard dose [0.6 mg/kg (maximum dose of 40 mg) every other week] or High dose [0.6 mg/kg (maximum dose of 40 mg) every week]).

Subjects will receive blinded treatment every week (ew) beginning at Week 8 and will remain on double-blinded therapy through Week 52.

- Subjects who are randomized to standard dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) every other week (eow) and will receive the matching placebo at the alternate week.
- Subjects who are randomized to high dose will receive a maintenance dose of 0.6 mg/kg (maximum dose of 40 mg) ew.
- Subjects who were randomized to placebo prior to Amendment 4 receive matching placebo ew.

Methodology (Continued):

Ongoing subjects randomized prior to Amendment 4 will continue their blinded treatment during the maintenance period until Week 52 and re-randomization to treatment for disease flare will be done according to Amendment 3 stipulations in these subjects.

At Week 8, subjects who have not achieved a clinical response per PMS will be discontinued. A safety evaluation call will be made 70 days after the last dose of study drug is administered to obtain follow-up information on any ongoing or new adverse events.

The duration of the study could be up to 66 weeks, which includes a Screening Period of up to 28 days, 8-week induction period and a 44-week double-blind maintenance period and a 70-day follow-up. Upon completion of the study, subjects will have the option to enroll into an open-label extension study where they will receive open-label adalimumab.

Treatment of Subjects with Disease Flare During the Study:

Criteria for Disease Flare are as follows:

- Subjects with a Week 8 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Week 8 score.
- Subjects with a Week 8 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Week 8 score.

Subjects will be expected to remain on blinded therapy throughout the 44-week maintenance period.

However, subjects with a disease flare, may be re-randomized to receive the following blinded-treatment at or after Week 12:

- Subjects who are randomized to Standard maintenance dose (0.6 mg/kg [maximum dose of 40 mg] eow) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume receiving the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
- Subjects who are randomized to High maintenance dose (0.6 mg/kg [maximum dose of 40 mg] ew) will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew).
- Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.

If a subject continues to meet the definition of disease flare (2nd time) following at least a 4-week course of blinded therapy since the subject has been re-randomized for disease flare, they may be switched to open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg]. *If a subject was re-randomized at Week 12 (to receive either re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]), then the earliest that subject could be evaluated to determine if the subject meets the criteria for disease flare for switch to OL (0.6 mg/kg [maximum of 40 mg]) weekly dosing is at Week 16.*

Methodology (Continued):

Treatment of Subjects with Disease Flare During the Study (Continued):

If a subject continues to meet the definition of disease flare (3rd time) following a 4-week course of open-label adalimumab every week at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab open-label 40 mg ew (maximum dose, not weight-based).

Subjects with persistent disease flare while on adalimumab 40 mg ew (max dose) may be withdrawn from the study at the investigator's discretion.

During open-label rescue therapy, subjects who are responders and have been in remission for at least 8 consecutive weeks (PMS \leq 2 with no individual subscore $>$ 1) may have their dosage decreased from ew to eow. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose de-escalation.

If subjects demonstrate disease flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to adalimumab ew dosing. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose re-escalation.

For subjects who meet the criteria for dose change, blood samples (adalimumab, AAA and hs-CRP) will be collected just prior to receiving any dose change (blinded therapy, escape to open-label adalimumab, dose de-escalation and dose re-escalation).

Subjects are allowed to be treated with stable doses of UC-related concomitant medications during the study, with the following exceptions and requirements:

- At or after Week 4, subjects taking corticosteroid therapy at Baseline may have their corticosteroid therapy tapered based on the investigator's discretion. A proposed tapering schedule is specified in Section 5.3.1.1.
- From Week 4 to Week 12, if the subject should experience an increase in symptoms after corticosteroid was tapered, the subject may have their corticosteroid dose increased back up to the corticosteroid dose at Baseline. This increase must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Subjects who experience disease flare at or after Week 12 are allowed to change their dose or initiate treatment with corticosteroids, immunosuppressant or 5-ASA; these increases must be discussed with and approved by the Medical Monitor prior to any changes in these treatments.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.
- Immunosuppressant therapy may be discontinued at or after Week 12 at the investigator's discretion.

At each study visit, in addition to routine physical examination including evaluation of extra intestinal manifestations and calculation of the PMS and PUCAI, the following will be collected:

- Anthropometric evaluations at Baseline, Week 26 and Week 52/Premature Discontinuation for determination of body mass index (BMI), and "z" scores for height and weight.
- IMPACT III Quality of Life questionnaire at Baseline, Week 8, Week 26 and Week 52/Premature Discontinuation Visit will be completed for subjects 9 years or older at the Baseline study visit.
- Bone age determination by x-ray of the wrist at Screening and at Week 52/Premature Discontinuation Visit in subjects who have not completed linear growth.
- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26 Week 34 and Week 52/Premature Discontinuation Visit and at Unscheduled Visit requiring dose change.

Methodology (Continued):

Treatment of Subjects with Disease Flare During the Study (Continued):

- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 8, Week 26 and Week 52/Premature Discontinuation Visit and at Unscheduled Visit requiring dose change.
- Tanner stage at Baseline, Week 26 and Week 52/Premature Discontinuation Visit.
- Endoscopy subscore at Screening and Week 52/Premature Discontinuation Visit.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subjects from the ages of 4 to 17 prior to baseline dosing.
2. Subjects with a diagnosis of UC for at least 12 weeks prior to screening confirmed by endoscopy with biopsy.

A colonoscopy will be performed during the screening period unless the subject underwent a colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis without evidence of dysplasia, colon cancer or infection). In this case the screening endoscopy may be either a colonoscopy or a flexible sigmoidoscopy.

If the subject underwent an endoscopy within 56 days of Baseline, and a video recording of the endoscopy is available, the video recording may be used and no additional endoscopy will be performed during the Screening period provided that the conditions noted in Section 5.3.1.1 are met and all technical requirements are fulfilled.

Note:

- If no appropriate documentation for confirmation of the diagnosis is available as per the investigator's judgment a diagnostic biopsy must also be performed.
 - Biopsies to rule out dysplasia, colon cancer and infection may be taken at the investigator's discretion.
3. Active ulcerative colitis with a Mayo Score of 6 – 12 points and endoscopy subscore of 2 – 3 (confirmed by central reader) despite concurrent treatment with at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):
 - Oral prednisone of ≥ 2 mg/day or equivalent, but not exceeding 40 mg/day, or oral budesonide ≥ 3 mg/day, but not exceeding 9 mg/day, with a stable dose for at least 7 days prior to Baseline; and/or
 - At least a consecutive 28-day course of azathioprine or 6-MP or methotrexate (MTX) prior to Baseline, with a stable dose prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of 230 – 450 pmol/ 8×10^8 RBC on the current dosing regimen or MTX ≥ 15 mg/m² body surface area/week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Note: If subjects are on both oral corticosteroid and immunosuppressants BOTH of the drugs need to meet the above criteria; and/or

- Concurrent therapy with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) is not required for subjects who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

4. Parent or guardian has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed or before any concomitant medication is discontinued for the purpose of this study. Pediatric subjects will be included in all discussions in order to obtain verbal and/or written assent.
5. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
6. Subject has a negative TB Screening Assessment.
If a subject has a positive (≥ 5 mm induration) PPD test and/or IGRA test at Screening, a CXR (PA and lateral view) must be performed for evaluation of active TB disease. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.
7. If female, subject who is either not of childbearing potential, defined as pre-menstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.
Examples of approved methods of birth control include the following (see local informed consent for more detail):
 - Total abstinence from sexual intercourse;
 - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
 - Hormonal contraceptives for 90 days prior to study drug administration;
 - A vasectomized partner.
8. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

Main Exclusion:

1. Subject with Crohn's disease (CD) or indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subjects with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Therapeutic enema or suppository within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of colectomy or subtotal colectomy (with ostomy) or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil, within 30 days prior to Baseline.
7. Female subjects who are breast-feeding or considering becoming pregnant during the study.
8. Positive pregnancy test at Screening or Baseline.
9. History of clinically significant drug or alcohol abuse in the last 12 months.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

10. Subjects on azathioprine or 6-mercaptopurine (6-MP) or MTX and subjects:
 - Have not been on stable doses of these medications for at least 28 days prior to Baseline; or
 - Have discontinued these medications within 28 days of Baseline.
11. Subjects on oral aminosalicylates who:
 - Have not been on stable doses of these medications for at least 14 days prior to Baseline; or
 - Have discontinued use of aminosalicylates within 14 days of Baseline.
12. Subjects on growth hormone who have not been on a stable dose for at least 4 weeks prior to Baseline.
13. Subjects on oral corticosteroids who:
 - Have not been on stable doses of these drugs for at least 7 days prior to Baseline; or
 - Discontinued use of oral corticosteroid within 14 days of Baseline; or
 - Have been taking both budesonide and prednisone (or equivalent) simultaneously.
14. Received intravenous corticosteroids within 5 days prior to Screening or during the Screening Period.
15. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.
16. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.
17. Previous treatment with adalimumab or previous participation in an adalimumab clinical study.
18. Positive *Clostridium difficile* (*C. difficile*) stool assay during the Screening Period.
19. Currently receiving total parenteral nutrition (TPN).
20. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
21. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).
22. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
23. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
24. Subject with a positive result for the Hepatitis B surface antigen (HBs Ag) or any HBV DNA PCR result that meets or exceeds detection sensitivity will be excluded.
25. Chronic recurring infections or active TB.
26. Subject has been treated with any investigational drug of chemical or biologic nature or any investigational procedure (including previous fecal transplantation) within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline Visit.
27. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
28. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab (Tysabri[®]) or efalizumab (Raptiva[®]) or rituximab (Rituxan[®]).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

29. Known hypersensitivity to adalimumab or its excipients.
30. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.

If the Screening endoscopy shows evidence of dysplasia or malignancy, subject may not be enrolled in the study.

31. Screening laboratory and other analyses show any of the following abnormal results:
 - ECG – with clinically significant abnormalities;
 - Aspartate transaminases (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range;
 - Total bilirubin ≥ 3 mg/dL;
 - Serum creatinine > 1.6 mg/dL;
 - Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Product:	Adalimumab
Induction Dose:	<p>Body weight adjusted induction dose regimen</p> <p>Prior to Amendment 4 subjects were randomized to receive one of 2 double-blind adalimumab induction doses.</p> <p><u>Standard Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and matching placebo at Week 1. Subjects received 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects received a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p> <p><u>High Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and Week 1. Subjects received 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects received a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p> <p>After Amendment 4 subjects will receive the open-label adalimumab high induction dose.</p> <p><u>High Induction Dose:</u> 2.4 mg/kg (maximum dose of 160 mg) at Week 0 and Week 1. Subjects will receive 1.2 mg/kg (maximum dose of 80 mg) at Week 2. At Weeks 4 and 6, subjects will receive a dosing regimen of 0.6 mg/kg (maximum dose of 40 mg).</p>

Double-Blind Maintenance Doses (in Week 8 PMS Responders only):	<p>Body weight adjusted maintenance dose regimen</p> <p><u>Blinded adalimumab Standard dosing regimen:</u> 0.6 mg/kg (maximum dose of 40 mg) eow with matching placebo at the alternate week</p> <p><u>Blinded adalimumab High dosing regimen:</u> 0.6 mg/kg (maximum dose of 40 mg) ew</p> <p>Subjects who were randomized to placebo (prior to Amendment 4) receive placebo ew.</p> <p>At or after Week 12 subjects who demonstrate a disease flare may be re-randomized to receive the following blinded-treatment.</p> <ul style="list-style-type: none"> • Subjects, who are randomized to standard maintenance dose, will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will resume to receiving the standard dose adalimumab (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule. • Subjects who are randomized to high maintenance dose, will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. The following week, all subjects will resume to receiving the high dose (0.6 mg/kg [maximum of 40 mg] ew). • Subjects who were randomized to placebo prior to Amendment 4 will be re-randomized to receive either adalimumab re-induction dose (2.4 mg/kg [maximum of 160 mg]) or to receive adalimumab (0.6 mg/kg [maximum of 40 mg]) at the visit. Afterwards, all subjects will receive the standard dose (0.6 mg/kg [maximum of 40 mg] eow) within the original dosing schedule.
Open-Label Maintenance Doses:	<p>High dose body weight adjusted.</p> <p>0.6 mg/kg (maximum dose of 40 mg) ew</p> <p>If a subject continues to meet the definition of disease flare following a 4-week course of open-label adalimumab ew at the dose 0.6 mg/kg [maximum of 40 mg], they may be switched to receive adalimumab 40 mg ew (maximum dose, not weight-based).</p>
Mode of Administration:	<p>Subcutaneous injection (SC)</p>
Reference Therapy:	<p>NA (after Amendment 4); Placebo (prior to Amendment 4)</p>
Dose:	<p>NA</p>
Mode of Administration:	<p>NA (after Amendment 4); Subcutaneous injection (SC) (prior to Amendment 4)</p>

Duration of Treatment: 52 weeks

- The subjects will visit the site at Screening, Baseline, Weeks 1, 2, 4, 8, 12, 18, 26, 34, 42, and 52/Premature Discontinuation and Unscheduled Visits.
- Subjects who qualify will be given the opportunity to enroll into an open-label study of the Long-term Safety and Tolerability of Repeated Administration of Adalimumab.

A 70-Day Follow-Up phone call will be completed for all subjects who either terminate early from the study or do not rollover into the extension study.

Criteria for Evaluation:

Efficacy analysis will be based on the Intent-To-Treat-Efficacy (ITT-E) population for the induction period and modified ITT (mITT) population for the maintenance period. The ITT-E population is a subpopulation of the ITT population, which consists of all subjects who received at least one SC injection of the study medication during the induction period. Subjects who receive open-label high induction dose, because they enrolled after Protocol Amendment 4 was released, will be excluded from the ITT-E population. The mITT population consists of all Week 8 PMS Responders among the ITT population who were randomized at Week 8 and received at least one SC injection of the study medication during maintenance period.

The safety analysis set will include all subjects who received at least one SC injection of the study medication.

Efficacy:

This study will utilize the Mayo Score, PMS and Mayo subscores to measure efficacy. The PUCAI will also be utilized as applicable. Please refer to 'Statistical Methods' for details on the sequentially rejective multiple test procedure of the dose groups used in this study versus external placebo for co-primary and ranked secondary endpoints.

Efficacy Endpoints

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1);
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo Score (defined as a Mayo Score ≤ 2 and no individual subscore > 1).

Ranked secondary efficacy endpoints are:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;
4. Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional exploratory secondary analyses:

- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 8;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI \geq 20 points from Baseline) at Week 8;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI \geq 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;
- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;
- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects in PMS response over time;
- Proportion of subjects in PMS remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points;
- Change from Baseline in hemoglobin, hematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with extraintestinal manifestations (EIM) at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy subscore of 0 or 1 (without friability) at Week 52;
- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without RBS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Change from Baseline in Mayo Score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy subscore at Week 52;
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

Pharmacokinetic:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline, Weeks 2, 4, 8, 12, 26, 34 and 52/Premature Discontinuation Visits, and at Unscheduled Visits requiring dose change. Blood samples will be collected for the measurement of serum anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Weeks 4, 8, 26 and 52/Premature Discontinuation Visits and at Unscheduled Visits requiring dose change. Blood samples will be collected for the measurement of serum Infliximab and HACA at Baseline (prior to dosing).

Safety:

Adverse events, laboratory data, and vital signs will be assessed at all visits throughout the study.

Statistical Methods:

Efficacy:

The efficacy analysis will be performed in the ITT-E set for the induction period and in the mITT set for the maintenance period. NRI method will be used to impute missing values for binary efficacy endpoints. Subjects who do not complete the induction period or who receive rescue therapy during the maintenance period will be considered as failures from that time point forward. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

The confirmatory efficacy analyses for the co-primary endpoints and ranked secondary endpoints are based on the following external placebo assumptions.

Statistical Methods (Continued):

External Placebo Assumptions for Co-Primary and Ranked Secondary Efficacy Endpoints

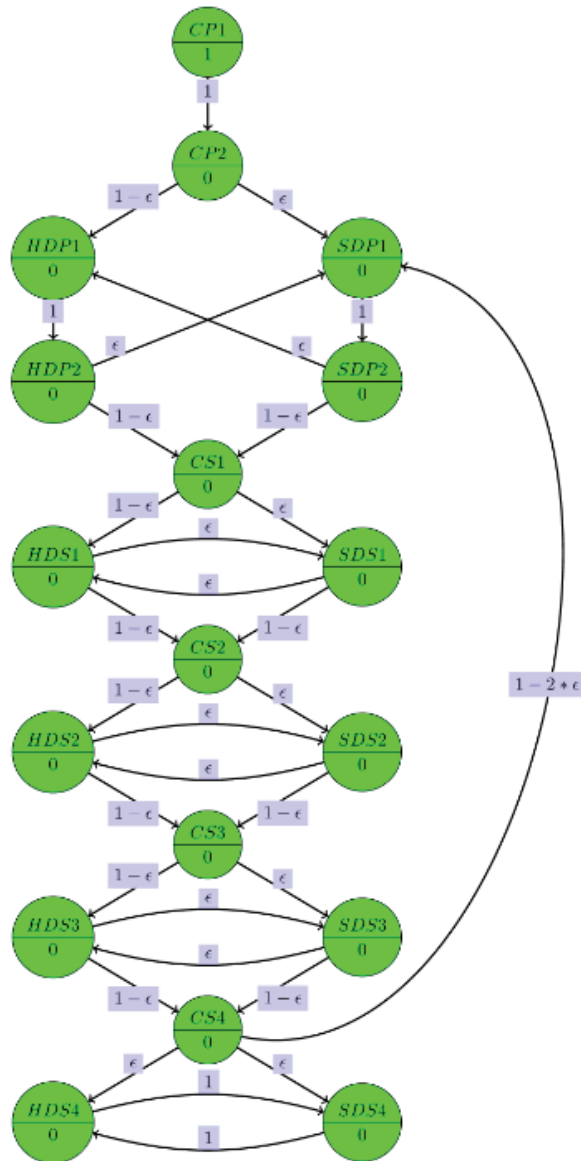
Endpoint	External Placebo Rate (95% CI Upper Limit from Meta-Analysis)
Week 8 PMS Remission	19.83%
Week 52 FMS Remission in Week 8 Responders per PMS	18.37%
Week 52 FMS Response in Week 8 Responders per PMS	26.10%
Week 52 Mucosal Healing in Week 8 Responders per PMS	22.03%
Week 52 FMS Remission in Week 8 Remitters per PMS	14.79%
Week 52 FMS Remission in Week 8 Responders per PMS with CS at Baseline and Discontinued CS prior to Week 52	24.08%

FMS = Full Mayo Score; PMS = Partial Mayo Score; CS = Corticosteroids

Co-primary and ranked secondary endpoints will be summarized by treatment group with 95% confidence intervals (CI) and adalimumab dose groups will be tested against external placebo in a sequentially rejective multiple test procedure in order to ensure that the multiple significance level of 5% is controlled, using one sample two-sided Chi-square tests. The below graph describes the structure of the multiple test procedure that starts with testing the co-primary endpoints for the combined high and standard adalimumab dose groups versus external placebo and then individual dose groups versus external placebo separately:

Statistical Methods (Continued):

Multiple Test Procedure for the Co-Primary and Ranked Secondary Endpoints



Assuming $\epsilon = 0.0005$; C = testing the endpoint for the combined high and standard adalimumab dose groups against external placebo; HD = testing the endpoint for the high adalimumab dose against external placebo; SD = testing the endpoint for the standard adalimumab dose against external placebo; P_1 = co-primary induction endpoint; P_2 = co-primary maintenance endpoint; S_i = ranked secondary endpoint i ($i=1, \dots, 4$)

Statistical Methods (Continued):

Additional exploratory secondary endpoints that are of the categorical type will be summarized by treatment group with 95% CIs. Additional exploratory secondary endpoints that are of the continuous type will be analyzed as changes from baseline, and reported by treatment group including 95% CIs.

The following subset of endpoints will be tested for the high adalimumab dose against the standard adalimumab dose in an exploratory manner:

- Proportion of subjects in PMS clinical remission at Week 8;
- Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission at Week 8;
- Proportion of subjects in PUCAI response at Week 8.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by treatment group at each time point using descriptive statistics. In addition, pharmacokinetic model based analyses will be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

AAA will be evaluated for each subject and each regimen, and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated. HACA will be evaluated for each subject and each regimen, and rates of HACA positive will be calculated.

Safety:

Treatment-emergent Adverse Events (AEs) and serious adverse events (SAEs) will be summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. A summary of AEs by severity and relationship to study drug will be performed. Changes in laboratory and vital sign data will be summarized using descriptive statistics. Shift tables will be provided.

Statistical Methods (Continued):

Sample Size:

The co-primary endpoints will be tested first for the combined high and standard adalimumab dose groups versus external placebo and then for the individual dose groups versus external placebo separately, controlling the multiple significance level of 5%. For each individual test the nominal power is calculated.

Assuming a 48% remission rate per PMS at Week 8 for the combined standard and high adalimumab induction dose groups and a remission rate per PMS of 19.83% for external placebo, a total of 77 subjects (high:standard = 46:31) in ITT-E population provides at least 99% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming a 36% remission rate per Mayo Score at Week 52 for the combined standard and high maintenance dose groups and a remission rate per Mayo Score of 18.37% for external placebo, a total of 57 subjects in the combined adalimumab maintenance dose groups in mITT population (e.g., high:standard = 28:29) provide 88% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming that the high adalimumab dose regimen is associated with higher efficacy than the standard adalimumab dose regimen, assuming a 52% remission rate per PMS at Week 8 for the high adalimumab induction dose group and a remission rate per PMS of 19.83% for external placebo, 46 subjects in the high adalimumab induction dose group of ITT-E population provide at least 99% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Assuming a 41% remission rate per Mayo Score at Week 52 for the high adalimumab maintenance dose group and a remission rate per Mayo Score of 18.37% for external placebo, a total of 28 subjects in the high adalimumab maintenance dose group of mITT population provide at least 80% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Based on the assumption of a 75% response rate at Week 8, 93 subjects will have to be included in the study (including ~12 internal placebo subjects in the maintenance part of the study who were included prior to Amendment 4) to ensure 57 subjects in the combined adalimumab maintenance dose groups.

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

Add:

EIM Extraintestinal manifestation

Section 3.2 Ulcerative Colitis and Current Treatments Overview

Last paragraph, first sentence previously read:

The safety and efficacy of adalimumab for the induction and maintenance of clinical remission in adult subjects with moderately to severely active UC has been studied in two completed clinical trials (Study M06-826 and Study M06-827) and an ongoing open-label study (Study M10-223).¹⁵⁻¹⁸

Has been changed to read:

The safety and efficacy of adalimumab for the induction and maintenance of clinical remission in adult subjects with moderately to severely active UC has been studied in two completed double-blind clinical trials (Study M06-826 and Study M06-827) and a completed open-label study (Study M10-223).¹⁵⁻¹⁸

Section 5.1 Overall Study Design and Plan: Description

First paragraph, first sentence previously read:

The study is designed to enroll approximately 85 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study is designed to enroll 93 subjects (not including the Japanese sub-study) to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.1 Overall Study Design and Plan: Description

Fourth paragraph previously read:

Approximately 85 pediatric subjects with moderate-to-severe ulcerative colitis (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3, confirmed by central reader) will be enrolled at approximately 50 sites worldwide (Section 5.3.1.1).

Has been changed to read:

93 pediatric subjects with moderate-to-severe ulcerative colitis (Mayo Score of 6 to 12 points with endoscopy subscore of 2 to 3, confirmed by central reader) will be enrolled at approximately 50 sites worldwide (Section 5.3.1.1).

Section 5.1 Overall Study Design and Plan: Description

Fifth paragraph, first sentence previously read:

There also will be up to approximately 20 Japanese subjects in a Japan sub-study to be enrolled at approximately 10 Japan sites.

Has been changed to read:

There also will be up to approximately 9 Japanese subjects in a Japan sub-study to be enrolled at approximately 10 Japan sites.

Section 5.3.2.1 Collection of Samples for Analysis

Subsection Collection of Samples for Adalimumab and AAA Assays

Fourth paragraph, last sentence previously read:

The number of samples planned is 680 (8 samples \times 85 subjects) for the adalimumab assay and 425 (5 samples \times 85 subjects) for the AAA assay for the entire study.

Has been changed to read:

The number of samples planned is 744 (8 samples \times 93 subjects) for the adalimumab assay and 465 (5 samples \times 93 subjects) for the AAA assay for the entire study.

Section 5.3.2.1 Collection of Samples for Analysis

Subsection Collection of Samples for Infliximab and HACA Assays

Last paragraph previously read:

The total number of samples planned will not exceed 170 (2 samples \times 85 subjects) for the entire study.

Has been changed to read:

The total number of samples planned will not exceed 186 (2 samples \times 93 subjects) for the entire study.

Section 5.3.3 Efficacy Variables

Add: new last paragraph

Please refer to Section 8.1.4 for details on the sequentially rejective multiple test procedure of the dose groups used in this study versus external placebo for co-primary and ranked secondary endpoints.

Section 5.3.3.1 Primary Variable

Section title and text previously read:

5.3.3.1 Primary Variable

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a $PMS \leq 2$ and no individual subscore > 1) in the high induction dose group as compared to external placebo.
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore > 1) in the high maintenance dose group as compared to external placebo.

External placebo data will be identified from an ongoing meta-analysis of relevant publically available clinical trials (see Section 8.1.4).

Has been changed to read:

5.3.3.1 Primary Variables

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a $PMS \leq 2$ and no individual subscore > 1);

2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore > 1).

Section 5.3.3.2 Secondary Variables

Previously read:

Ranked secondary efficacy variables are:

1. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS (high maintenance dose versus external placebo);
2. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS (high maintenance dose versus external placebo) (*);
3. Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
4. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo);
5. Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
6. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
7. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
8. Proportion of subjects in Partial Mayo clinical remission at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo);

9. Proportion of subjects in Partial Mayo clinical remission at Week 8 (standard induction dose versus external placebo);
10. Proportion of subjects in Mayo clinical remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo);
11. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore in Week 8 responders per PMS (standard maintenance dose versus external placebo);
12. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS (standard maintenance dose versus external placebo) (*);
13. Proportion of subjects in PUCAI remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
14. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo);
15. Proportion of subjects in PUCAI response at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
16. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
17. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo) (*);
18. Proportion of subjects in Partial Mayo clinical remission at Week 52 in Week 8 responders per PMS (standard maintenance dose versus external placebo);

(*) If external placebo data are not available, results will only be summarized by maintenance group and 95% CI will be provided.

Additional secondary variables are:

- Proportion of subjects in Partial Mayo clinical remission at Week 8 (high induction dose versus standard induction dose);
- Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in Mayo clinical response at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in Mayo clinical remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in Partial Mayo clinical remission at Week 52 (high maintenance dose versus standard maintenance dose);
- Proportion of subjects in PUCAI remission at Week 8 (high induction dose versus standard induction dose);
- Proportion of subjects in PUCAI response at Week 8 (high induction dose versus standard induction dose);
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;

- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;
- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects in Partial Mayo response over time;
- Proportion of subjects in Partial Mayo remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points;
- Change from Baseline in hemoglobin, hematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with extraintestinal manifestations (EM) at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy subscore of 0 or 1 (without friability) at Week 52;
- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;
- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);

- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
- Proportion of subjects in a 9 point Mayo (without RBS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS (high maintenance dose versus external placebo) (*);
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8 (high induction dose versus external placebo) (*);
- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8 (high induction dose versus external placebo) (*);
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8 (high induction dose versus external placebo) (*);
- Change from Baseline in Mayo score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy subscore at Week 52;
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

(*) If external placebo data are not available, results will only be summarized in the high maintenance or high induction dose group, respectively, and 95% CI will be provided.

Has been changed to read:

Ranked secondary efficacy variables are:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;

2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;
4. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Additional exploratory secondary analyses will be performed for:

- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 8;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 8;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Change from Baseline in total IMPACT III Quality of Life scores over time for subjects at least 9 years old at Baseline;
- Change from Baseline in WPAI scores over time;
- Change from Baseline in "z" scores for height (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) at Week 26 and Week 52;
- Change from Baseline in BMI at Week 26 and Week 52;
- Change from Baseline in "z" scores for weight-for-age at Week 26 and Week 52;

- Proportion of subjects at appropriate Tanner stage at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects in PMS response over time;
- Proportion of subjects in PMS remission over time;
- Proportion of subjects in PUCAI response over time;
- Proportion of subjects in PUCAI remission over time;
- Change from Baseline in number of daily stool over time;
- Change from Baseline in albumin and total protein at different time points;
- Change from Baseline in hemoglobin, hematocrit, red blood cell count at different time points;
- Change from Baseline in hs-CRP levels at different time points;
- Proportion of subjects with EIM at Week 26 and Week 52 compared to Baseline;
- Proportion of subjects with Mayo endoscopy subscore of 0 or 1 (without friability) at Week 52;
- Proportion of subjects being hospitalized during the study;
- Proportion of subjects undergoing colectomy during the study;
- Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and completed Week 52;
- Correlation between PMS and PUCAI at different time points;
- Proportion of subjects in a 9 point Mayo (without SFS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without PGA) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 9 point Mayo (without RBS) clinical remission (defined as ≤ 2 and no individual subscore > 1) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in a 6 point Mayo (without SFS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;

- Proportion of subjects in a 6 point Mayo (without PGA and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Proportion of subjects in a 6 point Mayo (without RBS and endoscopy subscore) clinical remission (defined as ≤ 1) at Week 8;
- Change from Baseline in Mayo score at Week 52;
- Change from Baseline in PMS over time;
- Change from Baseline in PUCAI over time;
- Change from Baseline in endoscopy subscore at Week 52;
- Change from Baseline in SFS over time;
- Change from Baseline in RBS over time;
- Change from Baseline in PGA over time.

Section 8.1.1 Analyzable Population

Second through fourth paragraph previously read:

Intent-To-Treat (ITT): Includes all randomized subjects who received at least one dose of the induction medication. ITT subjects will be analyzed as randomized. Subjects who have received open-label high induction dose will be excluded from the ITT population. ITT is the primary population for the induction period efficacy analyses.

Modified ITT (mITT): Consists of all Week 8 PMS Responders who were randomized at Week 8 and received at least one SC injection of the study medication during maintenance period. mITT is the primary population for the maintenance period efficacy analyses.

Re-Randomized population: Consists of all subjects with a disease flare who were re-randomized at or after Week 12 and received at least one SC injection of the study medication after the re-randomization.

Has been changed to read:

Intent-To-Treat (ITT): The ITT population includes all subjects who received at least one dose of the study medication during induction period. ITT subjects will be analyzed as randomized/enrolled.

ITT-E: The ITT-E population will be a subpopulation of the ITT population, where subjects who have received open-label high induction dose will be excluded. ITT-E is the primary population for the induction period efficacy analyses.

Modified ITT (mITT): Consists of all Week 8 PMS Responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period. mITT is the primary population for the maintenance period efficacy analyses.

Re-Randomized population: Consists of all subjects with a disease flare who were re-randomized at or after Week 12 and received at least one dose of the study medication after the re-randomization.

Section 8.1.2 Planned Methods of Statistical Analysis

Previously read:

All statistical tests will be two-sided with the significance level 0.05 except where indicated otherwise. Descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for continuous variables; and counts and percentages for discrete variables. The analysis will be performed using SAS[®] (SAS Institute Inc., Cary, NC, USA).

Has been changed to read:

Descriptive statistics will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for continuous variables; and counts and percentages for discrete variables. For confirmatory tests the multiple significance level of 0.05 will be controlled. The analysis will be performed using SAS[®] (SAS Institute Inc., Cary, NC, USA).

Section 8.1.4 Statistical Analyses of Efficacy

Previously read:

8.1.4 Statistical Analyses of Efficacy

8.1.4.1 Primary Efficacy Variable

The primary efficacy analysis will be performed in the ITT population for the Week 8 efficacy endpoints and in the mITT population for the Week 52 efficacy endpoint. Non-responder imputation (NRI) will be used to impute missing values for binary efficacy endpoints. Subjects who do not complete the induction period or who receive rescue therapy during the maintenance period will be considered as failures from that time point forward. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

The primary efficacy analysis for the co-primary endpoint at Week 8 is based on external placebo comparison identified from an ongoing meta-analysis of relevant publically available clinical trials. The lower limit of the 95% CI of the remission rate per PMS in the adalimumab high induction dose group in this study will be compared to the upper limit of the 95% CI of the corresponding external placebo rate. In order to demonstrate efficacy of adalimumab at Week 8 in the pediatric population, the lower limit of the 95% CI for the remission per PMS in the high induction dose group is required to be higher than the upper limit of the 95% CI of the remission rate of external placebo (assumptions based on adult UC studies Studies M06-826 and M06-827 are shown in for illustrative purposes only).

The primary efficacy analysis for the co-primary endpoint at Week 52 is based on the comparison of the high maintenance dose group versus external placebo using the approach described above.

Table 5. Placebo Data from Adult UC Studies

	Placebo Subjects by Prior Anti-TNF Status			
	Experienced n/N (%)	Naïve n/N (%)	Weighted Average for 25% Experienced +75% Naïve	
			%	95% CI Upper Limit
Week 8 Partial Mayo Remission (Pooled Study M06-826 and Study M06-827 IAS-E set ^a)	15/101 (14.9%)	61/367 (16.6%)	16.18%	19.52%
Week 52 Mayo Score Remission (Study M06-827 ITT set)	3/101 (3.0%)	18/145 (12.4%)	10.05%	13.81%

a. IAS-E data set consisted of all randomized subjects with confirmed UC who received at least 1 dose of blinded study drug in either Study M06-826 or Study M06-827.

8.1.4.2 Secondary Efficacy Variables

The secondary endpoints are divided into two groups. The first group consists of ranked secondary efficacy endpoints, which are ranked by hierarchical order and will be tested by a step down procedure. The second group includes all other secondary efficacy endpoints and special assessments.

Secondary endpoints that are of the binary type will be analyzed using 95% confidence intervals. Comparisons to external placebo will be done as described in Section 8.1.4.1. Comparisons between treatment groups will be done using ANOVA. The secondary endpoints that are of the continuous type will be analyzed as changes from baseline, and reported for the two treatment groups including 95% confidence intervals. Non-responder imputation (NRI) will be used to impute missing values for binary efficacy endpoints. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

Has been changed to read:

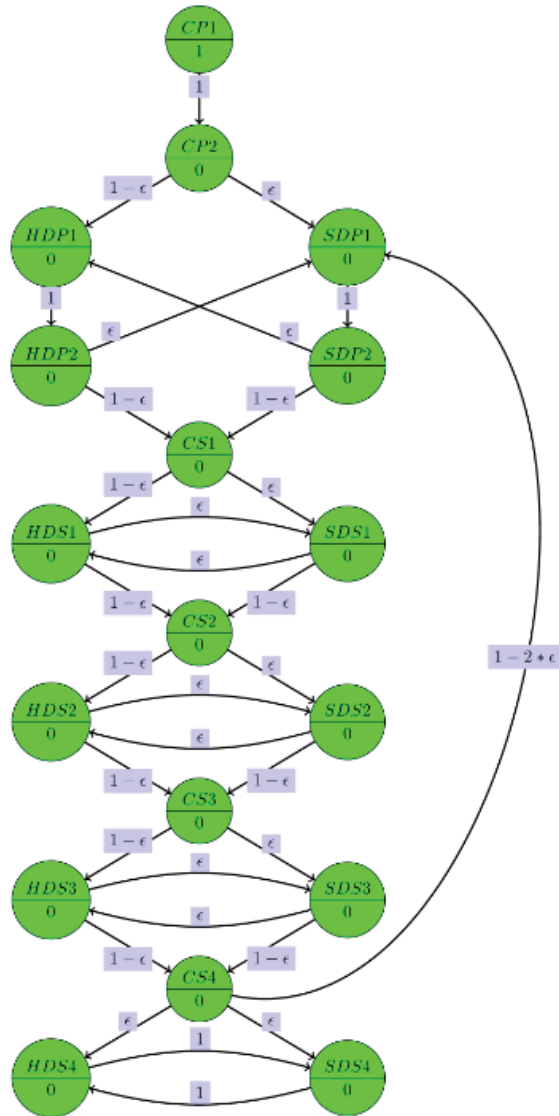
8.1.4 Statistical Analyses of Efficacy

The efficacy analysis will be performed in the ITT-E population for the Week 8 efficacy endpoints and in the mITT population for the Week 52 efficacy endpoints. Non-responder imputation (NRI) will be used to impute missing values for binary efficacy endpoints. Subjects who do not complete the induction period or who receive rescue therapy during the maintenance period will be considered as failures from that time point forward. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

8.1.4.1 Co-Primary and Ranked Secondary Efficacy Variables

Co-primary and ranked secondary endpoints will be summarized by treatment group with 95% confidence intervals (CI) and adalimumab dose groups will be tested against external placebo in a sequentially rejective multiple test procedure in order to ensure that the multiple significance level of 5% is controlled, using one sample two-sided Chi-square tests. The below graph describes the structure of the multiple test procedure that starts with testing the co-primary endpoints for the combined high and standard adalimumab dose groups versus external placebo and then individual dose groups versus external placebo separately:

Multiple Test Procedure for the Co-Primary and Ranked Secondary Endpoints



Assuming $\epsilon = 0.0005$; C = testing the endpoint for the combined high and standard adalimumab dose groups against external placebo; HD = testing the endpoint for the high adalimumab dose against external placebo; SD = testing the endpoint for the standard adalimumab dose against external placebo; P_1 = co-primary induction endpoint; P_2 = co-primary maintenance endpoint; S_i = ranked secondary endpoint i ($i = 1, \dots, 4$)

Section 8.1.4.3 contains details on assumed external placebo rates.

8.1.4.2 Additional Exploratory Secondary Efficacy Variables

Exploratory secondary endpoints that are of the binary type will be analyzed as proportions by treatment group including 95% CIs. Exploratory secondary endpoints that are of the continuous type will be analyzed as changes from baseline, and reported by treatment group including 95% CIs. Non-responder imputation (NRI) will be used to impute missing values for binary efficacy endpoints. Both LOCF and observed case analyses will be performed for continuous efficacy endpoints.

The following subset of endpoints will be tested for the high adalimumab dose against the standard adalimumab dose in an exploratory manner:

- Proportion of subjects in PMS clinical remission at Week 8;
- Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
- Proportion of subjects in PUCAI remission (defined as < 10) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline) at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects receiving corticosteroid at Baseline who discontinue corticosteroid prior to Week 52 and are in PUCAI remission at Week 52 in Week 8 responders per PMS;
- Proportion of subjects in PMS clinical remission at Week 52 in Week 8 responders per PMS;

- Proportion of subjects in PUCAI remission at Week 8;
- Proportion of subjects in PUCAI response at Week 8.

8.1.4.3 Derivation of External Placebo Control Rates

In order to derive robust external placebo assumptions for the co-primary and ranked secondary endpoints, a thorough literature search of placebo-controlled clinical studies in subjects with moderate to severe UC who had failed conventional therapy was performed. Studies M06-826 and M06-827 were the only available data sources with PMS data at Week 8. Studies GEMINI 1 and OCTAVE Sustain were the only studies with a similar subject population (i.e., failure or intolerance to prior corticosteroids or IMMs), study design (i.e., randomized withdrawal), and endpoint definitions for derivation of external placebo rates for the Week 52 endpoints in Study M11-290.

For all co-primary and ranked secondary endpoints where available, separate estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were derived as described by endpoint below. The estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were then combined as a weighted mean according to the assumed proportion of anti-TNF naïve and experienced subjects as per the Study M11-290 protocol, i.e., $0.75 \times \text{rate in anti-TNF naïve} + 0.25 \times \text{rate in anti-TNF experienced subjects}$. To be conservative, the upper limit of the 95% CI for the weighted mean was used as the external placebo assumption.

For PMS remission at Week 8: A remission rate of anti-TNF naïve placebo patients was estimated using logistic regression with anti-TNF naïve placebo patients from Studies M06-826 and M06-827 and study as a fixed effect, in order to weight the studies according to their sample sizes. Anti-TNF experienced placebo patients were only available in Study M06-827, so the remission rate from this study only was used as remission rate for anti-TNF experienced placebo patients.

For Mayo Score remission and mucosal healing at Week 52 in Week 8 responders per PMS, as well as for Mayo Score remission at Week 52 in Week 8 remitters per PMS:

Separate remission rates of anti-TNF naïve and anti-TNF experienced placebo patients were estimated using separate logistic regression models with anti-TNF naïve placebo patients and anti-TNF experienced placebo patients, respectively, from GEMINI 1 and OCTAVE Sustain and study as a fixed effect, in order to weight the studies according to their sample sizes.

For Mayo Score response Week 52 in Week 8 responders per PMS: Results were not available by anti-TNF naïve versus anti-TNF experienced placebo patients, so the overall response rates in placebo subjects from GEMINI 1 and OCTAVE Sustain were combined via logistic regression with study as a fixed effect, in order to weight the studies according to their sample sizes.

For steroid-free remission per Mayo Score at Week 52 in Week 8 responders per PMS with corticosteroids at Baseline: Only data from GEMINI 1 was available. Rates of anti-TNF naïve and anti-TNF experienced placebo patients from GEMINI 1 were combined to a weighted mean ($0.75 \times$ rate in anti-TNF naïve + $0.25 \times$ rate in anti TNF experienced subjects) and the upper bound of the 95% CI for the weighted mean was used.

Table 5. External Placebo Assumptions for Co-Primary and Ranked Secondary Efficacy Endpoints

Endpoint	External Placebo Rate (95% CI Upper Limit from Meta-Analysis)
Week 8 PMS Remission	19.83%
Week 52 FMS Remission in Week 8 Responders per PMS	18.37%
Week 52 FMS Response in Week 8 Responders per PMS	26.10%
Week 52 Mucosal Healing in Week 8 Responders per PMS	22.03%
Week 52 FMS Remission in Week 8 Remitters per PMS	14.79%
Week 52 FMS Remission in Week 8 Responders per PMS with CS at Baseline and Discontinuation of CS prior to Week 52	24.08%

FMS = Full Mayo Score; PMS = Partial Mayo Score; CS = Corticosteroids

Section 8.2 Determination of Sample Size

Previously read:

The sample size was calculated for the co-primary endpoints at Week 8 and Week 52. The Week 8 co-primary endpoint is to compare the lower limit of the 95% CI of the remission rate per PMS in the adalimumab high induction group in this study to the upper limit of the 95% CI of the corresponding external placebo rate to be identified from a meta-analysis of relevant publically available clinical trials. For illustrative purposes only, the following calculations use results from adult UC studies (Studies M06-826 and M06-827) as an estimate for the external placebo rates. Assuming a 48.33% remission rate per PMS at Week 8 for the high induction dose group and given an upper limit of the 95% CI for the remission rate per PMS of the external placebo of 19.52%, a sample size of 65 subjects (high:standard = 39:26) provides at least 97% power for a one sample two-sided Chi-square test using a significance level of 5% for the Week 8 co-primary endpoint.

The Week 52 co-primary endpoint is to compare the lower limit of the 95% CI of the remission rate per Mayo score in the adalimumab high maintenance dose group in this study to the upper limit of the 95% CI of the external placebo rate. Assuming a 36.63% remission rate per Mayo score at Week 52 for the high maintenance dose group and given an upper limit of the 95% CI for the remission rate per Mayo score of the external placebo of 13.81%, a sample size of 54 subjects (high:standard = 27:27) in the maintenance period of the study provides at least 85% power for a one sample two-sided Chi-square test using a significance level of 5% for the Week 52 co-primary endpoint.

Based on the assumption of a 75% response rate at Week 8, a total of 85 subjects are needed in the study (including internal placebo subjects enrolled prior to Amendment 4).

Sample Size Based on Week 8 and Week 52 Co-Primary Endpoints

Endpoints	External Placebo Upper 95% CI	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Induction Phase Sample Size
Week 8 PMS Remission Rate	19.52% ^a	48.33%	97%	39	Induction High:Standard 3:2 = 39:26	85 ^{b,c}
Endpoints	External Placebo Upper 95% CI	Assumption for High ADA Group	Power	N in High ADA Group	Randomization Ratio	Total Maintenance Phase Sample Size
Week 52 MS Remission Rate	13.81% ^a	36.63%	85%	27	Maintenance High:Standard 1:1 = 27:27	63 ^{b,d}

PMS = partial Mayo score; MS = full Mayo score

- The upper limit of 95% CI for placebo derived from adult UC Studies M06-826 and M06-827 for illustrative purposes only in the absence of results from the ongoing meta-analysis.
- Sample size calculation is based on a one group Chi-square test.
- 85 subjects are needed assuming 75% PMS response rate at Week 8.
- Including subjects enrolled into the internal placebo arm (prior to Amendment 4).

Has been changed to read:

The co-primary endpoints will be tested first for the combined high and standard adalimumab dose groups versus external placebo and then individual dose groups versus external placebo separately, controlling the multiple significance level of 5%. For each individual test the nominal power is calculated.

Assuming a 48% remission rate per PMS at Week 8 for the combined standard and high adalimumab induction dose groups and a remission rate per PMS of 19.83% for external placebo, a total of 77 subjects (high:standard = 46:31) in ITT-E population provides at least 99% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming a 36% remission rate per Mayo Score at Week 52 for the combined standard and high maintenance dose groups and a remission rate per Mayo Score of 18.37% for


external placebo, a total of 57 subjects in the combined adalimumab maintenance dose groups in mITT population (e.g., high:standard = 28:29) provide 88% power for a one sample two-sided Chi-square test using a significance level of 5%.

Assuming that the high adalimumab dose regimen is associated with higher efficacy than the standard adalimumab dose regimen and assuming a 52% remission rate per PMS at Week 8 for the high adalimumab induction dose group and a remission rate per PMS of 19.83% for external placebo, 46 subjects in the high adalimumab induction dose group of ITT-E population provide at least 99% power for a one sample two-sided Chi-square test using a significance level of 4.95%.


Assuming a 41% remission rate per Mayo Score at Week 52 for the high adalimumab maintenance dose groups and a remission rate per Mayo Score of 18.37% for external placebo, a total of 28 subjects in the high adalimumab maintenance dose group of the mITT population provide at least 80% power for a one sample two-sided Chi-square test using a significance level of 4.95%.

Based on the assumption of a 75% response rate at Week 8, 93 subjects will have to be included in the study (including ~12 internal placebo subjects in the maintenance part of the study who were included prior to Amendment 4) to ensure 57 subjects in the combined adalimumab maintenance dose groups.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
		Statistics
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
		Statistics
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Clinical