1.0 Title Page

Clinical Study Protocol M14-233

A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adalimumab for the Induction and Maintenance of Clinical Remission in Chinese Patients with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-reactive Protein

Incorporating Administrative Change 1 and Amendment 1

AbbVie Investigational Product:	Adalimumab
Date:	19 October 2015
Development Phase:	3
Study Design:	A randomized, double-blind, placebo controlled, multicenter study of the safety and efficacy of adalimumab in Chinese patients with moderately to severely active Crohn's disease
Investigators:	Multicenter study. Investigator's information is on file at AbbVie.
Sponsor:	AbbVie Inc.

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

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Section 1.0, Title Page, update Global Study Designated Physician.

  Rationale: *To provide contact information for the new Global Study Designated Physician.*

- Section 3.3, Adalimumab Overview, add additional approved adalimumab indications.

  Rationale: *To provide additional approved adalimumab indications.*

- Section 5.1, Overall Study Design and Plan: Description, Re-screening, clarify re-screening requirements for anti-HIV-1, HBV, and Anti-Hepatitis C testing.

  Rationale: *To clarify re-screening requirements in regards to anti-HIV-1, HBV, and Anti-Hepatitis C testing, and to reduce unnecessary testing.*

- Section 5.1, Overall Study Design and Plan: Description, Re-screening, update re-screening window for anti-HIV-1 repeat testing to 50 days.

  Rationale: *To align better with the seroconversion window of the immunoassay used by the central lab.*

- Section 5.2.1, Inclusion Criteria, add half tablet formulation language for azathioprine or 6-MP in Inclusion Criterion 4.

  Rationale: *To add that half-tablet formulations should be considered when rounding to determine azathioprine or 6-MP dose.*

- Section 5.2.2, Exclusion Criteria, remove efalizumab from Exclusion Criterion 12.

  Rationale: *To only reference available medications.*

- Section 5.2.2, Exclusion Criteria, clarify Exclusion Criterion 31 to exclude subjects with previous history of gastric dysplasia.

  Rationale: *To clarify that only gastric dysplasia and not dysplasia of the gastrointestinal tract is exclusionary to allow broader enrollment of patients.*

- Section 5.2.3.3, Prohibited Therapy, remove efalizumab from list of prohibited medications during study.

  Rationale: *To only reference available medications.*

- Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 1, Study Activities, table note "n.," clarify re-screening requirements for anti-HIV-1, HBV, and Anti-Hepatitis C testing.

  Rationale: *To clarify re-screening requirements in regards to anti-HIV-1, HBV, and Anti-Hepatitis C testing, and to reduce unnecessary testing.*

- Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 1, Study Activities, table note "n.," update re-screening window for anti-HIV-1 repeat testing to 50 days.

  Rationale: *To align better with the seroconversion window of the immunoassay used by the central lab.*

- Section 5.3.1.1, Study Procedures, Hepatitis and HIV Testing, clarify re-screening requirements for anti-HIV-1, HBV, and Anti-Hepatitis C testing.

  Rationale: *To clarify re-screening requirements in regards to anti-HIV-1, HBV, and Anti-Hepatitis C testing, and to reduce unnecessary testing.*

- Section 5.3.1.1, Study Procedures, Hepatitis and HIV Testing, update re-screening window for anti-HIV-1 repeat testing to 50 days.

  Rationale: *To align better with the seroconversion window of the immunoassay used by the central lab.*

- Section 5.3.1.2, Blood Samples for Pharmacogenetic Analysis, clarify that an AbbVie designated laboratory in China will perform testing and long-term storage.

  Rationale: *To clarify that an AbbVie designated laboratory in China will perform testing and long-term storage of pharmacogenetic samples.*

- Section 5.3.1.3, Blood Samples for Biomarkers Analysis, clarify that an AbbVie designated laboratory in China will perform testing and long-term storage.

  Rationale: *To clarify that an AbbVie designated laboratory in China will perform testing and long-term storage of biomarker samples.*

- Section 5.3.5, Pharmacokinetic Variables, add section.

  Rationale: *To specify further the pharmacokinetic variables being studied.*

- Section 5.4.1, Discontinuation of Individual Subjects, clarify to withdraw subjects if dysplasia occurs.

  Rationale: *To clarify that dysplasia and not specifically dysplasia of the gastrointestinal tract will require subjects to be withdrawn from the study.*

- Section 5.4.1, Discontinuation of Individual Subjects, add that information regarding any ongoing or new AEs/SAEs will be recorded on the appropriate eCRF page.

  Rationale: *To provide further details on how data for any ongoing or new AEs/SAEs gathered during the 70-day follow-up phone call will be captured*

- Section 6.1.5, Adverse Event Reporting, update Primary Study Designated Physician.

  Rationale: *To provide contact information for the new Primary Study Designated Physician.*

- Section 6.1.5, Adverse Event Reporting, clarify adverse event reporting process preferred route and update local pharmacovigilance contact information.

  Rationale: *To clarify adverse event reporting process preferred route and provide new contact information for local pharmacovigilance.*

- Section 7.0, Protocol Deviations, clarify that AbbVie does allow deviations when necessary to eliminate an immediate hazard to study subjects.

  Rationale: *To ensure study sites can deviate from the protocol when necessary if in the best interest of the study subjects.*

- Appendix B, List of Protocol Signatories, update Associate Medical Director, remove Program Lead I, and add Study Management Associate III.

  Rationale: *To list the new Associate Medical Director signatory and replace Program Lead I with Study Management Associate III as signatory*.

- Appendix D, Standard Weights, update references to actual height to adjusted height.

  Rationale: *To clarify that the height used to determine standard weight for CDAI scoring is adjusted to include one inch or 2.5 cm.*

- Appendix E, Sample Injection Instructions for Onsite Administration – Pre-Filled Syringe, add measurement references in cm.

Rationale: *To provide measurements in local units.*

- Appendix F, Sample Injection Instructions for at Home Dosing – Pre-Filled Syringe, add measurement references in cm.

  Rationale: *To provide measurements in local units.*

- Incorporate administrative changes, correct typographical and grammatical errors and make further clarifications throughout the protocol.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-233
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 19 October 2015
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adalimumab for the Induction and Maintenance of Clinical Remission in Chinese Patients with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-reactive Protein	
Objectives: The primary objective of this study is to assess the efficacy and safety of adalimumab in inducing (at Week 4) and maintaining (at Week 26 in Week 8 responders) clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150, in Chinese subjects with moderately to severely active CD and elevated hs-CRP. **Additional Objectives:** To assess the effect of adalimumab treatment on other efficacy outcomes, including clinical response, steroid free remission, and improvement in quality of life.	
Investigators: Multicenter in China	
Study Sites: Approximately 12 – 15 sites in China	
Study Population: Chinese males and females 18 to 70 years (inclusive) of age with moderately to severely active CD and elevated (≥ 3 mg/L) high-sensitivity C-reactive protein who are naïve to anti-TNF therapy.	
Number of Subjects to be Enrolled: Approximately 200 (100 in active group and 100 in placebo group).	
Methodology: This is a Phase 3, randomized, double-blind, placebo controlled, multicenter study of adalimumab in anti-TNF naïve Chinese subjects with moderately to severely active CD (220 ≤ Crohn's disease activity index [CDAI] ≤ 450) and elevated hs-CRP (≥ 3 mg/L). The study consists of an 8-week double-blinded period followed by an open-label (OL) period of 18 weeks. Subjects will be randomized in a 1:1 ratio to receive adalimumab or placebo at Baseline. Subjects randomized to adalimumab at Week 0 will receive blinded adalimumab 160 mg at Week 0, 80 mg at Week 2, and blinded 40 mg adalimumab and placebo at Week 4 and Week 6. Subjects randomized to placebo at Week 0 will receive blinded placebo at Week 0 and Week 2, then will receive blinded adalimumab 160 mg at Week 4 and 80 mg at Week 6. At Week 8, all subjects will enroll in an 18-week OL period to receive adalimumab 40 mg every other week (eow).	

Methodology (Continued):

Adalimumab Treatment Regimen (Double-Blind Period)			Placebo Treatment Regimen (Double-Blind Period)		
Study Visit	**Number of Active Syringes**	**Number of Placebo Syringes**	**Study Visit**	**Number of Active Syringes**	**Number of Placebo Syringes**
Week 0 – 160 mg ada	4	0	Week 0 – placebo	0	4
Week 2 – 80 mg ada	2	0	Week 2 – placebo	0	2
Week 4 – 40 mg ada	1	3	Week 4 – 160 mg ada	4	0
Week 6 – 40 mg ada	1	1	Week 6 – 80 mg ada	2	0

ada = adalimumab

Note: At Week 8, study drug will be administered during the OL Period of the study.

The study duration will be up to 39 weeks, and will include a screening period of up to 35 days, an 8-week double-blind treatment period, an 18-week OL period and a 70-day follow-up period. 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. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation. All subjects will be screened for tuberculosis (TB) during the Screening period and throughout the trial.

TB Screening consists of:

- QuantiFERON-TB Gold In-Tube test (QTF)
- CXR (chest CT scan can be used instead of CXR at the Investigator's discretion)
- Medical history of contact with active TB

If any of the three assessments (QTF, CXR/CT, or medical history) is positive during the Screening Period, the subject will be considered to have latent TB infection (LTBI) and will receive TB prophylaxis.

For subjects with an indeterminate QTF result during the Screening period, a repeat Screening period test should be performed with another blood sample or the subject must initiate TB prophylaxis prior to enrolling in the study. If the repeat testing result during the Screening period is negative the QTF test result is considered negative, but if the repeat testing result is indeterminate or positive TB prophylaxis should be initiated.

In the assessment of the Screening CXR/chest CT scan, a radiologist must note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB as well as the presence of hilar and/or mediastinal lymphadenopathy. The Principal Investigator must indicate the clinical significance of any findings and contact the AbbVie SDP to discuss any clinically significant abnormal findings before enrolling the subject. The Principal Investigator (or designee) will sign and date each report.

Subjects who have a diagnosis of LTBI during Screening and do not initiate prophylaxis cannot be enrolled.

Methodology (Continued):

Subjects who have a diagnosis of LTBI and agree to initiate prophylaxis should be consulted with a TB specialist (a physician with TB treatment knowledge and experience) regarding the selection of the appropriate TB prophylaxis regimen as per Centers for Disease Control (CDC) recommendations or local guidelines.

Initiation of TB prophylaxis in subjects with negative LTBI screening is permitted during the Screening period as warranted based on the opinion of the investigator.

Subjects with an LBTI diagnosis or those in whom TB prophylaxis is electively initiated will receive TB prophylaxis for at least 21 days (before or on the Day –21 visit) prior to Baseline (Week 0), and are required to have a Day –21 and Day –7 visits. At Day –21, the CDAI and hs-CRP must be obtained and must meet the entry criteria in Section 5.2. For the calculation of the CDAI on Day –21, the hematocrit value obtained at the first screening visit will be used. After initiation of TB prophylaxis, subjects will return to the clinical site 7 days (at Day –7) prior to Baseline (Week 0) to have safety labs drawn, including hs-CRP. The hematocrit and hs-CRP values obtained at Day –7 will be used to calculate the Baseline (Week 0) CDAI to confirm eligibility for study enrollment.

All subjects will be monitored for signs and symptoms suggestive of active TB at all visits. Additional QTF and chest imaging testing will be performed throughout the study as outlined below:

Chart for TB Assessments at Screening and After Week 0

Screening Period				After Week 0	
				Monitoring For:	
QTF	CXR/CT	Medical History	TB Prophylaxis Required	LTBI	Active TB
+	+	+	Yes	No	Yes^
+	+	-	Yes	No	Yes^
+	-	+	Yes	No	Yes^
+	-	-	Yes	No	Yes^
-	+	+	Yes	No	Yes^
-	-	+	Yes	No	Yes^
-	+	-	Yes	No	Yes^
-	-	-	No	Yes*	Yes^

* During follow-up, subjects who are negative for LTBI during screening and are not taking TB prophylaxis will have their QTF repeated at Weeks 2, 4, 6, 8, 12, 16, 20, and 26/Premature Discontinuation and the chest imaging repeated at Weeks 8, 16, and 26/Premature Discontinuation. Subjects who are negative for LBTI during Screening who initiate TB prophylaxis per the Investigator's discretion do not require repeat QTF testing.

^ All subjects will be monitored for signs and symptoms suggestive of active TB at all visits. CXR (or chest CT, at the Investigator's [or designee's] discretion) will be repeated Weeks 8, 16, and 26/Premature Discontinuation. If there are signs or symptoms suggestive of active TB, and/or changes in the chest imaging, a diagnostic investigation must be done.

Methodology (Continued):

All subjects who initiate TB prophylaxis should continue the prophylaxis regimen for the duration of the subject's participation in the study, including the 70-day follow-up period.

The randomization will be stratified by Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline (Week 0) and systemic corticosteroid use at Baseline.

All subjects will have blood samples drawn for the measurement of adalimumab concentration immediately prior to dosing at Baseline (Week 0), and Weeks 4, 8, 12, and 26/Premature Discontinuation and anti-adalimumab antibody (AAA) levels just prior to dosing at Baseline (Week 0), Weeks 4, 12 and 26/Premature Discontinuation. If a subject meets the criteria for dose escalation, blood samples will also be obtained for adalimumab concentration and AAA levels at the time of dose escalation. Pre-dosing serum samples for infliximab concentration and human antichimeric antibodies (HACAs) will be collected at Baseline (Week 0). An optional mRNA sample and an optional pharmacogenetic sample will be drawn prior to dosing at Baseline and Week 26/Premature Discontinuation (only if subject discontinues at or after Week 8).

At Week 4, all subjects who are on oral steroids will have their steroid dose tapered according to the schedule in Section 5.3.1.1. The steroid taper is mandatory and deviations from the taper (or increases in steroid doses) are not permitted. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the subject must be withdrawn from the study.

If a subject who has tapered their corticosteroid dose is judged by the Investigator to have an inadequate response per the PI's judgment, dose escalation (allowed at or after Week 12) should be considered if the subject meets the below criteria, otherwise, the subject should be withdrawn from the study.

For the purposes of dose escalation, inadequate response is defined as:

Crohn's disease activity index (CDAI) ≥ 200 and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or a hs-CRP ≥ 5 mg/L. The hs-CRP results used to determine inadequate response should be the most recent available results. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation. The most recent hs-CRP value should first be assessed in relation to the most recent CDAI from the previous visit. Then the most recent hs-CRP value should be assessed in relation to CDAI calculated at the current visit. Dose changes are to only occur in accordance with the eow dosing schedule.

At or after Week 12, any subject who experiences inadequate response may increase dose to OL adalimumab 80 mg eow. If the subject has received OL 80 mg eow therapy and continues to demonstrate inadequate response, he or she should be withdrawn from the study per PI discretion.

Additionally, 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 the designated study visits. For any subject with clinical signs/symptoms of active TB or newly identified TB risk factors, a CXR/chest CT scan (per investigator discretion) may be required for evaluation of active TB, and it is recommended to contact the SDP for further guidance. Subjects with confirmed active TB must be discontinued from the study and receive standard of care based on consultation with a local TB specialist (a physician with TB treatment knowledge and experience).

Methodology (Continued):

During the Screening and Double-Blind Periods, in addition to the TB screening described above, the following tests will be performed. Laboratory tests (hematologic and chemical analysis, including hs-CRP) will be performed during Screening and at Weeks 0, 2, 4, and 8/Premature Discontinuation. Urinalysis will be performed at Screening and Weeks 0, 4, and 8/Premature Discontinuation. Serum will be collected during the Screening Period for testing for anti-nuclear antibodies (ANA) and reflective anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies.

During the OL period, in addition to the TB screening described above, laboratory tests (hematologic and chemical analysis, including hs-CRP) will be performed during study visits at Weeks 12, 16, 20, and 26/Premature Discontinuation, and urinalysis will be performed at Weeks 12, 20, and 26/Premature Discontinuation.

AEs will be collected during the study and for 70 days after the last study drug administration.

Crohn's Disease Activity Index (CDAI) will be obtained during the Screening Period and at Weeks 0, 2, 4, 6, 8, 12, 16, 20, and 26/Premature Discontinuation. If the subject doses onsite then the CDAI will also be completed at Weeks 10, 14, 18, 22, and 24. The inflammatory bowel disease questionnaire (IDBQ) will be administered at Weeks 0, 4, 8, and 26/PD.

Subjects should adhere to the required visit schedule. Study visits should occur within the ± 3 day visit window. The Baseline visit at Week 0 should occur within 35 days of the Screening visit.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female of Chinese descent with full Chinese parentage 18 to 70 years (inclusive) of age at Baseline (Week 0).
2. Confirmed diagnosis of Crohn's disease for at least 3 months prior to Baseline (Week 0). Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Subject has hs-CRP ≥ 3 mg/L in all laboratory measurements during the Screening Period.
4. Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450 at Baseline (Week 0) despite concurrent or prior treatment with an adequate course, in the opinion of the investigator, of at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):
    - Subjects taking oral corticosteroids, excluding budesonide:
        - Oral corticosteroid dose must be ≤ 20 mg/day (prednisone or equivalent);
            - For subjects with a dose > 10 and ≤ 20 mg/day, dose has been stable for at least 7 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline.
            - For subjects with a dose ≤ 10 mg/day, dose has been stable for at least 10 days prior to Baseline (Week 0) and the duration of the current steroid course has been at least 14 days prior to Baseline (Week 0).
    - Subjects taking oral budesonide:
        - Dose must not exceed 9 mg/day;
            - For subjects with a dose ≥ 6 mg/day, dose has been stable for at least 7 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline.

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

Main Inclusion (Continued):

- For subjects with a dose < 6 mg/day, dose has been stable for at least 10 days prior to Baseline (Week 0) and the duration of the current steroid course has been at least 14 days prior to Baseline (Week 0).

and/or,

- At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of azathioprine ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or MTX ≥ 15 mg/week (subcutaneous [SC]/intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.
  - Subject must be on a stable dose for at least 28 days prior to Baseline (Week 0).
    - For subjects taking azathioprine, the dose should not exceed 3 mg/kg/day.
    - For subjects taking 6-MP, the dose should not exceed 1 mg/kg/day.
    - For subjects taking IM/SC MTX, dose should not exceed 25 mg per week.
    - Note: Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline), however use of oral MTX is not sufficient for inclusion into the study.

  Note: If a subject is on both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria.

and/or

- Concurrent therapy with corticosteroids or the above-mentioned immunosuppressants (azathioprine, 6-MP or IM/SC MTX) is not required for subjects not currently taking these medications who were previously treated during the past 2 years 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.

5. Subject has a negative TB Screening Assessment. If the subject has evidence of a latent TB infection during the Screening Assessment, the subject must initiate and complete a minimum of 3 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis prior to Baseline (Section 5.3.1).
6. If female subject, is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) 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):

   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
   - Hormonal contraceptives for 90 days prior to study drug administration;
   - A vasectomized partner.
7. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.

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

Main Inclusion (Continued):

8. Subject is judged to be in otherwise good health as determined by the Principal Investigator (or designee) based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead electrocardiogram (ECG) performed during Screening.
9. Subject must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis (UC) or indeterminate colitis.
2. Subject who has discontinued azathioprine or 6-MP or MTX or another immunomodulator within 14 days of Baseline (Week 0), or, for subjects taking oral MTX or another immunomodulator, has not been on a stable dose for at least 28 days prior to Baseline.
3. Subject who has discontinued use of oral aminosalicylates within 14 days of Baseline (Week 0) or, for subjects taking oral aminosalicylates, has not been on a stable dose for at least 28 days prior to Baseline.
4. Subject taking both oral budesonide and oral prednisone (or equivalent) simultaneously, with the exception of non-systemic steroids (e.g., inhalers or dermatological preparations), during the Screening Period and during the study.
5. Subject taking intravenous corticosteroids within 14 days prior to Screening, during the Screening Period, or who has discontinued oral corticosteroids within 14 days before Baseline (Week 0).
6. Subject who has had a surgical bowel resection within 6 months of Screening or who is planning a resection at any time point in the future.
7. Subject with symptomatic known obstructive strictures.
8 Subject with an internal or external fistula (with the exception of an anal fistula without abscess).
9. Subject with an ostomy or ileoanal pouch.
10. Subject with short bowel syndrome.
11. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to Screening and/or during the Screening period.
12. Subject with prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®] or rituximab [Rituxan®]).
13. Subject has been treated with any investigational agent or procedure (including previous fecal microbial transplantation) within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline (Week 0) Visit.
14. Previous participation in an adalimumab clinical study. Prior exposure to any anti-tumor necrosis factor (TNF) agent (including but not limited to branded or biosimilar versions of adalimumab [Humira®], infliximab [Remicade®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®), tocilizumab (Actemra®), anakinra (Kineret®), abatacept (Orencia®) or vedolizumab (Entyvio®).
15. Subject taking Crohn's-related antibiotics who has been on this therapy to treat an active infection or who has not been on stable doses of these medications for at least 14 days prior to Baseline.

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

Main Exclusion (Continued):

16. Subject has received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline (Week 0).
17. Active infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline (Week 0) Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
18. Subject currently receiving total parenteral nutrition (TPN) during Screening and/or at Baseline (Week 0) or subject who plans to receive TPN at any time during the course of the study.
19. Subject with positive Clostridium difficile (C. *difficile*) toxin stool assay during the Screening period.
20. Subject has received any systemic traditional Chinese medicine preparation within 14 days before Baseline (Week 0).
21. Subject has received any thalidomide within 28 days before Baseline (Week 0).
22. Screening laboratory and other analyses show any of the following abnormal results (if a subject starts TB prophylaxis, lab results [except ECG] should be confirmed at Day –7):
    - AST, ALT > 1.5 × upper limit of the reference range;
    - WBC count < 3.0×10^9/L;
    - Electrocardiogram (ECG) – with clinically significant abnormalities;
    - Total bilirubin ≥ 3 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Serum creatinine > 1.6 mg/dL.
23. Known hypersensitivity to adalimumab or its excipients.
24. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
25. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency virus (HIV) or active TB.
26. Subject with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
27. Positive anti-HIV-1 antibody (HIV-1 Ab), unless the screening anti-HIV-1 antibody is subsequently found to be negative on confirmatory testing; and/or positive Hepatitis C virus antibody (HCV Ab) indicative of a previous or current infection; and/or positive Hepatitis B surface antigen (HBs Ag) or detected sensitivity on the Hepatitis B (HBV)-DNA polymerase chain reaction test for Hepatitis B core antibody (HBc Ab Total) positive subjects. If Hepatitis B envelope antigen and antibodies (HBe Ag or HBe Ab) are detected, it is per investigator discretion to enroll the subject.
28. Chronic recurring infections or Active TB.

    Active TB is considered to be:
    - Subject with CXR (or chest CT scan) findings suggestive of active TB as determined by a radiologist;
    - Subject with any clinical symptoms consistent with active TB;
    - With or without micobacteriology/histology examination for Mycobacterium tuberculosis or granulomas.

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

Main Exclusion (Continued):

29. Subjects with any findings indicating a history of TB infection (calcified nodules or granulomas and/or fibrotic scar, apical or basilar thickening) by CXR examination (or chest CT scan) at the screening evaluation and no documentation of prophylactic treatment.
30. 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.
31. Subject with a previous history of gastric dysplasia.
32. Positive pregnancy test at Screening or Baseline (Week 0).
33. Female subjects who are breastfeeding or considering becoming pregnant during the study.
34. History of clinically significant drug or alcohol abuse, including use of medical marijuana, in the last 12 months.
35. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
36. Current evidence of dysplasia or a 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.
37. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Product:	Adalimumab (40 mg/0.8 mL)
Doses:	**8-Week Double-Blind Period:** Adalimumab 160 mg at Week 0, 80 mg at Week 2, 40 mg at Weeks 4 and 6, or Matching placebo at Week 0 and at Week 2, 160 mg at Week 4, and 80 mg at Week 6. **18-Week Open-Label Treatment Period:** Adalimumab 40 mg eow starting at Week 8 through Week 26. If subject qualifies for dose escalation during the OL Period, the subject may escalate to adalimumab 80 mg eow.
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment: The study will include a Screening Period of up to 35 days, a double-blind 8-week Treatment Period, and an Open-Label Treatment Period for 18 weeks for all subjects followed by a 70-day follow-up period from the last dose of study drug for subjects who complete the study or discontinue from the study prematurely. The 70-day follow-up call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 4.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Secondary Endpoints:

The Week 26 Efficacy Endpoint:

Proportion of subjects who achieve clinical remission at Week 26 (CDAI < 150) in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

Key Secondary Endpoints:

- Proportion of subjects who achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 4.
- Proportion of subjects who achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who achieved decrease in CDAI ≥ 70 points from Baseline plus at least 30% reduction in hs-CRP from Baseline at Week 8.
- Proportion of subjects who discontinue corticosteroid use and achieve clinical remission (CDAI < 150) at Week 26 in subjects who were taking steroids at Baseline and who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.
- Proportion of subjects who discontinue corticosteroid use and achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who were taking steroids at Baseline and who achieved decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 8.
- Proportion of subjects who achieve clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 4.
- Proportion of subjects who achieve decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 4.
- Proportion of subjects who achieve CDAI < 150 and hs-CRP < 3 mg/L at Week 4.
- Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.
- Proportion of subjects who achieve IBDQ remission (IBDQ ≥ 170 points) at Week 4.
- Proportion of subjects who achieve IBDQ remission at Week 26 in subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.
- Change from Baseline in fecal calprotectin level at Week 4.
- Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L and fecal calprotectin < 250 µg/g at Week 4.
- Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L and fecal calprotectin < 250 µg/g at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

Additional Secondary Endpoints:

- Proportion of subjects with clinical remission (CDAI < 150) over time.
- Proportion of subjects with CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline over time.
- Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline over time.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline over time.

Criteria for Evaluation (Continued)

Efficacy (Continued):

Additional Secondary Endpoints (Continued):

- Change from Baseline in CDAI over time.
- Change from Baseline in hs-CRP level over time.
- Change from Baseline in fecal calprotectin level over time.

Additional analyses are outlined in the protocol.

Pharmacokinetic:

Blood samples will be collected for the measurement of serum adalimumab concentration just prior to dosing at Baseline (Week 0), Weeks 4, 8, 12, and Week 26/Premature discontinuation and AAA just prior to dosing at Baseline (Week 0), Week 4, Week 12, and Week 26/Premature Discontinuation. If a subject meets the criteria for dose escalation, blood samples will also be obtained for adalimumab concentration and AAA levels at the time of dose escalation.

Blood samples will also be collected for measurement of infliximab serum levels and HACA just prior to dosing at Baseline (Week 0).

Safety:

Safety analyses will be performed on all subjects who receive at least one dose of study drug. Incidence of adverse events, changes in vital signs, physical examination results, and clinical laboratory data will be assessed.

Statistical Methods:

Efficacy:

The primary efficacy variable is the proportion of subjects with moderately to severely active CD who have achieved clinical remission, defined as CDAI < 150, at Week 4. The comparison between treatment groups for the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline and corticosteroid use at Baseline (Yes/No). A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. The ITT set includes all subjects who were randomized at baseline. Missing CDAI at Week 4 will be imputed using the non-responder imputation (NRI) approach.

For Week 26 efficacy endpoint, the one sample Exact test will be performed and the two-sided 95% CI will be provided. Rates of remission at Week 26 will be evaluated in patients meeting the definition for response (reduction in CDAI ≥ 70 points from Baseline) after induction therapy (determined at Week 8) and compared against a clinically meaningful remission rate obtained using the data from adult placebo from the Western CD Study M02-404 (see Section 8.2 for details). For key and additional secondary efficacy endpoints, continuous variables will be analyzed using Analysis of Covariance (ANCOVA) model including factor for treatment group, stratification factors and Baseline values, whereas CMH test stratified by stratification factors used for discrete endpoints at Week 4 and one sample Exact test for discrete endpoints at Week 26. NRI for missing data will be used for categorical endpoints. Both last observation carried forward (LOCF) and observed case analyses will be performed for continuous endpoint. The LOCF analysis is considered primary for inferential purposes.

Statistical Methods (Continued):

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 positivity will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment emergent adverse events may be evaluated.

Safety:

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety summary statistics will be provided by treatment groups. Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 70 days after the last dose of the study medication. Treatment-emergent AEs will be summarized separately for the double-blind dosing period (Week 0 to Week 8) and the OL period (Week 8 to 70 days after the last dose of the study medication). The number and percent of subjects experiencing AEs will be tabulated by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA) preferred term for each treatment group.

Changes in laboratory data will be described using statistical characteristics and summarized by treatment group. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

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
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDC	Centers for Disease Control and Prevention
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-reactive protein
CT	Computerized tomography
CXR	Chest x-ray
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eow	every other week
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HACA	Human Anti-Chimeric Antibody
HBV	Hepatitis B virus
HBc Ab Total	Hepatitis B core antibody
HBe Ab	Hepatitis B envelope antibody
HBe Ag	Hepatitis B envelope antigen
HBs Ab	Hepatitis B surface antibodies
HBs Ag	Hepatitis B surface antigen

HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
IGRA	Interferon-Gamma Release Assay
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JIA	Juvenile Idiopathic Arthritis
LTBI	Latent Tuberculosis Infection
MedDRA	Medical Dictionary for Drug Regulatory Activities
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NRI	Non-responder Imputation
OL	Open-Label
PA	Poster-anterior
PK	Pharmacokinetics
POR	Proof of Receipt
PPD	Purified protein derivative
Ps	Psoriasis
PsA	Psoriatic Arthritis
RA	Rheumatoid arthritis
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SDP	Study designated physician
TB	Tuberculosis
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
UC	Ulcerative Colitis
WBC	White blood cell

Definition of Terms

Clinical Remission	CDAI < 150
Clinical Response	Decrease in CDAI ≥ 70 points from Baseline
Inadequate Response (for determining eligibility for dose escalation)	Crohn's disease activity index (CDAI) ≥ 200 at any one visit and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L. The hs-CRP results used to determine inadequate response should be the most recent available results. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation. The most recent hs-CRP value should first be compared to the most recent CDAI from the previous visit. Then the most recent hs-CRP value should be assessed in relation to CDAI calculated at the current visit. Dose changes are to only occur in accordance with the eow dosing schedule.

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3.0 Introduction

Crohn's disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract.[1] The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups.[1,2] In North America, the incidence of CD is estimated to be 3.1 to 14.6 cases per 100,000 persons.[1] Prevalence rates range from 26 to 99 cases per 100,000 persons. In Europe, CD has an incidence of 0.7 to 9.8 cases per 100,000 persons and a prevalence of 8.3 to 214 cases per 100,000 persons.[1]

The incidence of CD in Asia is lower than that in the West, ranging from 0.14 to 1.22 cases per 100,000 persons.[3-5] Until recently, CD was not considered a public health problem in Asia, perhaps in part to the lack of accurate epidemiological data in Asia. However, CD disease location is broadly similar to that reported in Western studies and complex disease behavior (defined as stricturing, penetrating, or perianal disease) is present in a high proportion of patients, which has implications for the need for medical and surgical treatments in this part of the world.[6]

Guidelines for the management of CD from the Chinese Cooperative Group for the study on IBD recommend the use of aminosalicylates or antibiotics for mild disease, and steroids or immunomodulators (AZA, 6-mercaptopurine [6-MP], or methotrexate [MTX]) for moderate disease.[7] Infliximab is recommended for severe or refractory disease. A recent publication reported that short-term infliximab treatment (5 mg/kg at Weeks 0, 2, and 6) was effective to induce remission in Chinese patients with CD who had failed standard therapies.[8] Because infliximab requires administration in an infusion setting, which may be inconvenient, and because many patients lose response or become intolerant to infliximab over time, additional options are necessary for patients in China with CD.

3.1 Differences Statement

This study is being conducted to evaluate the safety and efficacy of adalimumab in Chinese subjects with moderately to severely active CD and elevated high-sensitivity C-reactive protein (hs-CRP). While numerous studies have been conducted on the use of adalimumab for treatment of moderately to severely active CD, to date no Phase 3 adalimumab efficacy and safety CD studies have been conducted in China.

3.2 Benefits and Risks

Extensive clinical and post-marketing experience exists with adalimumab in a wide range of disease states including CD and ulcerative colitis (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 CD have not altered this safety profile and demonstrated a positive benefit/risk balance. Conditions which may present a risk specifically for patients with CD are exclusion criteria in this study (e.g., evidence of colonic dysplasia or active infections).

3.3 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant deoxyribonucleic acid (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 tumor necrosis factor (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).

Tumor necrosis factor (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 United States (US) and European Union (EU) for the treatment of Rheumatoid Arthritis (RA) in 2002 and 2003, respectively. Additional indications have been approved in the US and EU including Psoriasis (Ps), Psoriatic Arthritis (PsA), Ankylosing Spondyloarthritis (AS), CD, Ulcerative Colitis (UC), polyarticular Juvenile Idiopathic Arthritis (JIA), pediatric CD, pediatric psoriasis as well as pediatric Enthesitis Related Arthritis and non-radiographic axial spondyloarthritis in the EU, and intestinal Bechet's Disease in Japan. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

3.4 Safety Information

Adalimumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for RA. 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 a United States Food and Drug Administration (FDA)-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in patients who are 30 years of age 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.

4.0 Study Objectives

The primary objective of this study is to assess the efficacy and safety of adalimumab in inducing (at Week 4) and maintaining (at Week 26 in Week 8 responders) clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150, in Chinese subjects with moderately to severely active CD and elevated hs-CRP.

Additional objectives are to assess the effect of adalimumab treatment on other efficacy outcomes, including clinical response, steroid free remission, and improvement in quality of life.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo controlled, multicenter study of adalimumab in anti-TNF naïve Chinese subjects with moderately to severely active CD (220 ≤ Crohn's disease activity index [CDAI] ≤ 450) and elevated hs-CRP (≥ 3 mg/L). The study consists of an 8-week double-blinded period followed by an open-label (OL) period of 18 weeks. Subjects will be randomized in a 1:1 ratio to receive adalimumab or placebo at Baseline. Subjects randomized to adalimumab at Week 0 will receive blinded adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and Week 6. Subjects randomized to placebo at Week 0 will receive blinded placebo at Week 0 and Week 2, then will receive blinded adalimumab 160 mg at Week 4 and 80 mg at Week 6. At Week 8, all subjects will enroll in an 18-week OL period to receive adalimumab 40 mg every other week (eow). No drug will be administered at the final study visit.

The study was designed to enroll approximately 200 subjects 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.

The study duration will be up to 39 weeks, and will include a screening period of up to 35 days, an 8-week double blind treatment period, an 18-week OL period and a 70-day follow-up period. 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. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation. All subjects will be screened for latent tuberculosis infection (LTBI) during the Screening period and for LTBI and active TB throughout the trial.

In order to be eligible for randomization, the subject must have met all of the inclusion criteria and none of the exclusion criteria of the protocol.

The randomization will be stratified by Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline (Week 0) and systemic corticosteroid use at Baseline.

Adalimumab Treatment Regimen (Double-Blind Period)			**Placebo Treatment Regimen (Double-Blind Period)**		
Study Visit	**Number of Active Syringes**	**Number of Placebo Syringes**	**Study Visit**	**Number of Active Syringes**	**Number of Placebo Syringes**
Week 0 – 160 mg ada	4	0	Week 0 – placebo	0	4
Week 2 – 80 mg ada	2	0	Week 2 – placebo	0	2
Week 4 – 40 mg ada	1	3	Week 4 – 160 mg ada	4	0
Week 6 – 40 mg ada	1	1	Week 6 – 80 mg ada	2	0

ada = adalimumab

Note: At Week 8, study drug will be administered during the OL Period of the study.

All subjects will have blood samples drawn for the measurement of adalimumab concentration immediately prior to dosing at Baseline (Week 0), and Weeks 4, 8, 12, and 26/Premature Discontinuation and anti-adalimumab antibody (AAA) levels just prior to dosing at Baseline (Week 0), Weeks 4, 12, and 26/Premature Discontinuation. If a subject meets the criteria for dose escalation, blood samples will also be obtained for adalimumab concentration and AAA levels at the time of dose escalation. Pre-dosing serum samples for infliximab concentration and human antichimeric antibodies (HACAs) will be

collected at Baseline (Week 0). An optional mRNA sample and an optional pharmacogenetic sample will be drawn prior to dosing at Baseline and Week 26/Premature Discontinuation (only if subject discontinues at or after Week 8).

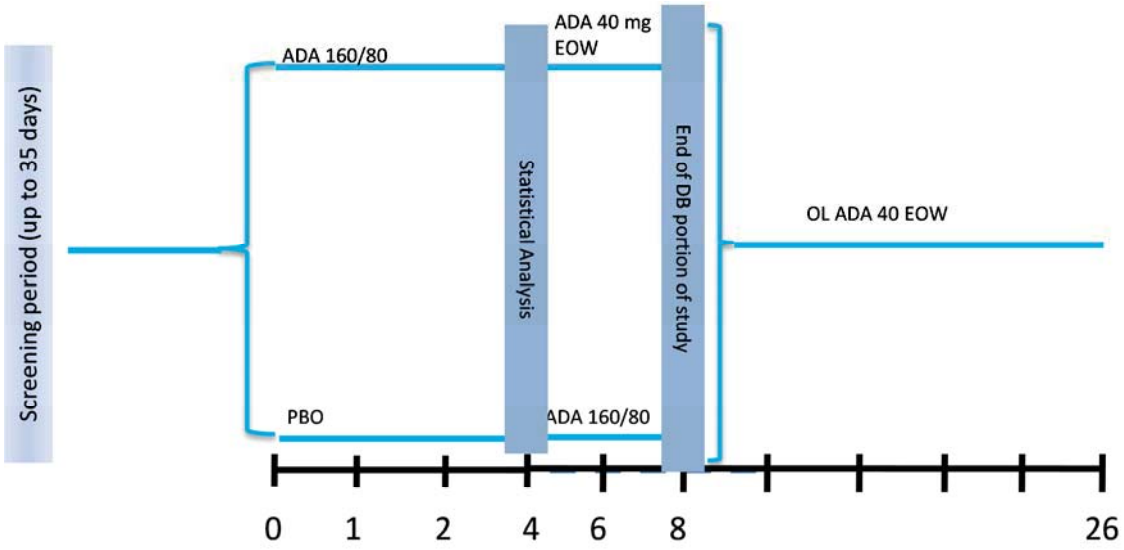
At Week 4, all subjects who are on oral steroids will have their steroid dose tapered according to the schedule in Section 5.3.1.1. The steroid taper is mandatory and deviations from the taper (or increases in steroid doses) are not permitted. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the subject must be withdrawn from the study. If a subject who has tapered their corticosteroid dose is judged by the Investigator to have an inadequate response per the PI's judgment, dose escalation (allowed at or after Week 12) should be considered if the subject meets the below criteria, otherwise, the subject should be withdrawn from the study.

For the Purposes of Dose Escalation, Inadequate Response is Defined as:

Crohn's disease activity index (CDAI) ≥ 200 and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L. The hs-CRP results used to determine inadequate response should be the most recent available results. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation. The most recent hs-CRP value should first be compared to the most recent CDAI from the previous visit. Then the most recent hs-CRP value should be assessed in relation to CDAI calculated at the current visit. Dose changes are to only occur in accordance with the eow dosing schedule.

At or after Week 12, any subject who experiences inadequate response may increase dose to OL adalimumab 80 mg eow. If the subject has received OL 80 mg eow therapy and continues to demonstrate inadequate response, he or she should be withdrawn from the study per PI discretion.

Figure 1. Study Design



Subjects may discontinue adalimumab treatment at any time during study participation. Subjects who end study participation early will have a Premature Discontinuation Visit. All subjects who do not initiate adalimumab therapy not supplied in the context of the clinical trial after the end of study participation 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. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

Re-screening

Subjects who initially screen fail for the study are 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 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 QuantiFERON-TB Gold In-Tube test,

CXR (or optional chest CT scan), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met. If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors. If the subject had negative HBV and Anti-Hepatitis C test results from the central lab, these tests will not be required to be repeated if the results were obtained within 35 days of the re-screening visit. As appropriate, sites are encouraged to contact the AbbVie SDP to confirm if subjects should or should not be re-screened.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Male or female of Chinese descent with full Chinese parentage 18 to 70 years (inclusive) of age at Baseline (Week 0).
2. Confirmed diagnosis of Crohn's disease for at least 3 months prior to Baseline (Week 0). Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Subject has hs-CRP ≥ 3 mg/L in all laboratory measurements during the Screening Period.
4. Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450 at Baseline (Week 0) despite concurrent or prior treatment with an adequate course, in the opinion of the investigator, of at least one of the following (oral corticosteroids or immunosuppressants or both as defined below):
    - Subjects taking oral corticosteroids, excluding budesonide:
        - Oral corticosteroid dose must be ≤ 20 mg/day (prednisone or equivalent);
            - For subjects with a dose > 10 and ≤ 20 mg/day, dose has been stable for at least 7 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline.

- For subjects with a dose ≤ 10 mg/day, dose has been stable for at least 10 days prior to Baseline (Week 0) and the duration of the current steroid course has been at least 14 days prior to Baseline (Week 0).

- Subjects taking oral budesonide:
  - Dose must not exceed 9 mg/day;
    - For subjects with a dose ≥ 6 mg/day, dose has been stable for at least 7 days prior to Baseline and the duration of the current steroid course has been at least 14 days prior to Baseline.
    - For subjects with a dose < 6 mg/day, dose has been stable for at least 10 days prior to Baseline (Week 0) and the duration of the current steroid course has been at least 14 days prior to Baseline (Week 0).

and/or,

- At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of azathioprine ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or MTX ≥ 15 mg/week (subcutaneous [SC]/intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.
  - Subject must be on a stable dose for at least 28 days prior to Baseline (Week 0).
    - For subjects taking azathioprine, the dose should not exceed 3 mg/kg/day.
    - For subjects taking 6-MP, the dose should not exceed 1 mg/kg/day.
    - For subjects taking IM/SC MTX, dose should not exceed 25 mg per week.
    - Note: Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline), however use of oral MTX is not sufficient for inclusion into the study.

  Note: If a subject is on both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria.

and/or

- Concurrent therapy with corticosteroids or the above-mentioned immunosuppressants (azathioprine, 6-MP or IM/SC MTX) is not required for subjects not currently taking these medications who were previously treated during the past 2 years 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.

5. Subject has a negative TB Screening Assessment. If the subject has evidence of a latent TB infection during the Screening Assessment, the subject must initiate and complete a minimum of 3 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis prior to Baseline (Section 5.3.1).

6. If female subject, is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) 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):

   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
   - Hormonal contraceptives for 90 days prior to study drug administration;
   - A vasectomized partner.

7. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.

8. Subject is judged to be in otherwise good health as determined by the Principal Investigator (or designee) based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead electrocardiogram (ECG) performed during Screening.

9. Subject must be able and willing to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections.

5.2.2 Exclusion Criteria

1. Subject with a current diagnosis of ulcerative colitis (UC) or indeterminate colitis.
2. Subject who has discontinued azathioprine or 6-MP or MTX or another immunomodulator within 14 days of Baseline (Week 0), or, for subjects taking oral MTX or another immunomodulator, has not been on a stable dose for at least 28 days prior to Baseline.
3. Subject who has discontinued use of oral aminosalicylates within 14 days of Baseline (Week 0) or, for subjects taking oral aminosalicylates, has not been on a stable dose for at least 28 days prior to Baseline.
4. Subject taking both oral budesonide and oral prednisone (or equivalent) simultaneously, with the exception of non-systemic steroids (e.g., inhalers or dermatological preparations), during the Screening Period and during the study.
5. Subject taking intravenous corticosteroids within 14 days prior to Screening, during the Screening Period and during the study, or who has discontinued oral corticosteroids within 14 days before Baseline (Week 0).
6. Subject who has had a surgical bowel resection within 6 months of Screening or who is planning a resection at any time point in the future.
7. Subject with symptomatic known obstructive strictures.
8. Subject with an internal or external fistula (with the exception of an anal fistula without abscess).
9. Subject with an ostomy or ileoanal pouch.
10. Subject with short bowel syndrome.
11. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to Screening and/or during the Screening period.
12. Subject with prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including

participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®] or rituximab [Rituxan®]).

13. Subject has been treated with any investigational agent or procedure (including previous fecal microbial transplantation) within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline (Week 0) Visit.

14. Previous participation in an adalimumab clinical study. Prior exposure to any anti-tumor necrosis factor (TNF) agent (including but not limited to branded or biosimilar versions of adalimumab [Humira®], infliximab [Remicade®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®), tocilizumab (Actemra®), anakinra (Kineret®), abatacept (Orencia®) or vedolizumab (Entyvio®).

15. Subject taking Crohn's-related antibiotics who has been on this therapy to treat an active infection or who has not been on stable doses of these medications for at least 14 days prior to Baseline.

16. Subject has received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline (Week 0).

17. Active infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline (Week 0) Visit or oral anti-infectives within 14 days prior to the Baseline Visit.

18. Subject currently receiving total parenteral nutrition (TPN) during Screening and/or at Baseline (Week 0) or subject who plans to receive TPN at any time during the course of the study.

19. Subject with positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening period.

20. Subject has received any systemic traditional Chinese medicine preparation within 14 days before Baseline (Week 0).

21. Subject has received any thalidomide within 28 days before Baseline (Week 0).

22. Screening laboratory and other analyses show any of the following abnormal results (if a subject starts TB prophylaxis, lab results [except ECG] should be confirmed at Day –7):
    - AST, ALT > 1.5 × upper limit of the reference range;
    - WBC count < 3.0×10^9/L;
    - Electrocardiogram (ECG) – with clinically significant abnormalities;
    - Total bilirubin ≥ 3 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Serum creatinine > 1.6 mg/dL.
23. Known hypersensitivity to adalimumab or its excipients.
24. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
25. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency virus (HIV) or active TB.
26. Subject with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
27. Positive anti-HIV-1 antibody (HIV-1 Ab), unless the screening anti-HIV-1 antibody is subsequently found to be negative on confirmatory testing; and/or positive Hepatitis C virus antibody (HCV Ab) indicative of a previous or current infection; and/or positive Hepatitis B surface antigen (HBs Ag) or detected sensitivity on the Hepatitis B (HBV) DNA polymerase chain reaction test for Hepatitis B core antibody (HBc Ab Total) positive subjects. If Hepatitis B envelope antigen and antibodies (HBe Ag or HBe Ab) are detected, it is per investigator discretion to enroll the subject.
28. Chronic recurring infections or Active TB.

    Active TB is considered to be:
    - Subject with CXR (or chest CT scan) findings suggestive of active TB as determined by a radiologist;

- Subject with any clinical symptoms consistent with active TB;
- With or without micobacteriology/histology examination for Mycobacterium tuberculosis or granulomas.

29. Subjects with any findings indicating a history of TB infection (calcified nodules or granulomas and/or fibrotic scar, apical or basilar thickening) by CXR examination (or chest CT scan) at the screening evaluation and no documentation of prophylactic treatment.
30. 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.
31. Subject with a previous history of gastric dysplasia.
32. Positive pregnancy test at Screening or Baseline (Week 0).
33. Female subjects who are breastfeeding or considering becoming pregnant during the study.
34. History of clinically significant drug or alcohol abuse, including use of medical marijuana, in the last 12 months.
35. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
36. Current evidence of dysplasia or a 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.
37. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, and/or vitamins) that the subject is receiving at the time of screening, or receives during the

study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate eCRF.

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

5.2.3.1 Prior Therapy

Crohn's disease specific medications (including but not limited to CD-related antibiotics, corticosteroids, aminosalicylates and immunomodulators) that the subject has received within 90 days of Baseline (Week 0) should be recorded on the appropriate page of the eCRF and should include the dates of administration and dosages and frequency.

Subjects who are not currently taking a corticosteroid or immunomodulator (specifically, azathioprine, 6-MP or SC/IM MTX) require confirmed documentation of failure to respond within the past 2 years or lack of tolerability within the past 5 years.

- For subjects with failure to respond to treatment with corticosteroids or immunomodulators (specifically, azathioprine, 6-MP or SC/IM MTX) within the past 2 years, the dates (start and end dates) of the most recent course of treatment, the maximum daily dosage of the most recent course of treatment, and reason(s) for discontinuation are to be recorded in the appropriate eCRF.

In addition, the highest known dose taken within the past 2 years will be recorded.

- For subjects who were intolerant to treatment with corticosteroids or immunomodulators (specifically, azathioprine, 6-MP or SC/IM MTX) within the past 5 years, the dates (start and end dates) of the most recent course of treatment, the maximum daily dosage of the most recent course of treatment, and reason(s) for discontinuation are to be recorded in the appropriate eCRF. In addition, the highest known dose taken within the past 5 years will be recorded in appropriate eCRF.

In addition, if subjects have/had ever been treated with azathioprine, 6-MP, or MTX (oral or IM/SC), the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will also be recorded in appropriated eCRF.

5.2.3.2 Concomitant Therapy

Subjects taking immunomodulators at Baseline will continue their dose of azathioprine, 6-MP, MTX or any other immunomodulators during the study, provided they are on a stable dose of the medication for at least 28 days prior to Baseline (Week 0). Doses of these concomitant medications (azathioprine, 6-MP, MTX, or other immunomodulators) must remain stable throughout the duration of the study, 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.

Subjects taking aminosalicylates at Baseline will continue aminosalicylates during the study, provided they are on stable doses of the medication for at least 28 days prior to Baseline (Week 0). Doses of oral aminiosalicylates must remain stable throughout the duration of the study, except in the event of treatment-related toxicities considered moderate to severe in the opinion of the investigator.

Subjects taking corticosteroids at Baseline will continue their dose of corticosteroids during the study, provided they are on a stable dose prior to Baseline (Week 0) as outlined in inclusion criterion 4 in Section 5.2.1. Subjects will not be permitted to change the

corticosteroid dose during the first 4 weeks of the study, except in the event of treatment-related toxicities considered moderate to severe in the opinion of the investigator. At Week 4, all subjects will have their dose tapered according to the schedule in Section 5.3.1.1. The steroid taper is mandatory and deviations from the taper (or increases in steroid doses) are not permitted. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the subject must be withdrawn from the study.

- For steroids other than budesonide, a reduction of 5 mg prednisone (or equivalent) per day for doses > 10 mg/day of prednisone (or equivalent) every week until a 10 mg/day (or equivalent) dose is reached, then a weekly decrease by 2.5 mg (or equivalent) per day until discontinuation.
- For budesonide, a weekly decrease by 3 mg/day of budesonide until discontinuation.

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

Subjects taking CD-related antibiotics at Baseline will continue stable doses of CD-related antibiotics during the study, provided they are on a stable dose of the medication for at least 14 days prior to Baseline (Week 0). No changes to the dose at Baseline (Week 0) will be allowed except for treatment related toxicities or concerns about development of antibiotic resistance.

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

Setons are authorized as concomitant therapy in subjects with perianal fistulas and should be documented in the CRF under concomitant medications.

The AbbVie SDP 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:

- All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following branded or biosimilar versions of:
  - Etanercept (Enbrel®);
  - Infliximab (Remicade®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Golimumab (Simponi®);
  - Certolizumab pegol (Cimzia®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Vedolizumab (Entyvio®);
- Live vaccines (during the study and for 70 days after the last dose of study drug);
- Thalidomide.

Rectal therapy with any therapeutic enemas or suppositories, other than required for endoscopy, is prohibited within 14 days prior to and during the Screening Period and during the study.

Intravenous corticosteroid use is prohibited within 14 days prior to Screening, during the Screening Period and during the study.

Use of cyclosporine, tacrolimus, or mycophenolate mofetil is prohibited within 30 days prior to Baseline (Week 0) and during the study.

Tofacitinib (Xeljanz®) is prohibited during the study.

Use of any systemic traditional Chinese medicine preparation within 14 days before Baseline (Week 0) and throughout the study.

Investigational agents or procedures (including fecal microbial transplantation) are prohibited within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline (Week 0) and during the study.

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

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in Section 5.3.1.1. All subjects must meet the study selection criteria outlined in Section 5.2.1 and Section 5.2.2 in order to be randomized in to the study.

Table 1. Study Activities

Activity	Screening (35 Days)	Day –21[a]	Day –7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Informed Consent	X																		
Inclusion/Exclusion[d]	X	X	X	X															
Medical/Surgery History[d]	X			X															
Alcohol and Tobacco Use	X																		
Previous and Concomitant Medication[d]	X	X	X	X	X	X	X	X	X[y]	X	X[y]	X	X[y]	X	X[y]	X[y]	X	X	
Vital Signs[e]	X			X	X	X	X	X	X[y]	X	X[y]	X	X[y]	X	X[y]	X[y]	X	X	
Dispense Subject CDAI Diary[f]	X																		
Physical Examination[g]	X			X	X	X	X	X						X			X	X	
Physician TB evaluation	X	X	X	X	X	X	X	X	X[y]	X	X[y]	X	X[y]	X	X[y]	X[y]	X	X	
TB Screening[h]	X				X	X	X	X		X		X		X			X		
Chest x-ray[i]	X							X				X					X		
Initiate TB Prophlyaxis[j]		X																	
ECG[k]	X																		

Table 1. Study Activities (Continued)

Activity	Screening (35 Days)	Day –21[a]	Day –7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Chemistry and Hematology	X		X	X	X	X	X	X		X		X		X			X	X	
Urinalysis[l]	X		X	X		X		X		X				X			X	X	
Pregnancy Tests[m]	X			X													X	X	
Hepatitis B Screen, HCV, and HIV[n]	X																		
hs-CRP	X		X	X	X	X	X	X		X		X		X			X	X	
C. *difficile* toxin	X																		
Antinuclear antibody (ANA)/ Anti-double-stranded DNA (anti ds-DNA)[o]	X																		
Stool Sample (fecal calprotectin)				X		X		X									X		
Human Antichimeric Antibodies (HACA)/ Infliximab Concentrations				X															
Adalimumab Concentration[p]				X		X		X		X	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[p]		
AAA Concentration[p]				X		X				X	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[p]		

Table 1. Study Activities (Continued)

Activity	Screening (35 Days)	Day –21[a]	Day –7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Optional Pharmacogenetic Marker[r]				X													X^{s}		
Optional biomarker mRNA[r]				X													X^{s}		
Crohn's Disease Activity Index (CDAI)		X		X	X	X	X	X	X^{y}	X	X^{y}	X	X^{y}	X	X^{y}	X^{y}	X	X	
Start Corticosteroid Taper[t]						X													
Monitor Adverse Events[u]	X	X	X	X	X	X	X	X	X^{y}	X	X^{y}	X	X^{y}	X	X^{y}	X^{y}	X	X	X
Study Drug Dispensing/ Administration[v]				X	X	X	X	X	X^{w}	X	X^{w}	X	X^{w}	X	X^{w}	X^{w}		X^{x}	
Inflammatory Bowel disease Questionnaire (IBDQ)				X		X		X									X		

a. Day – 21 and Day –7 visits are required for subjects who initiate TB prophylaxis during the screening period. If a subject does not initiate TB prophylaxis, these visits are not required.

b. The Baseline (Week 0) visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits.

c. Subjects will be contacted 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects who initiate adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

d. Update inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information to assure subject eligibility.

e. Height will be measured at Screening only.

Table 1. Study Activities (Continued)

f. Diary should be brought back to the site at every visit.

g. Physical examination performed at Screening, Week 4, Week 8, and Week 26/Premature Discontinuation Visits are full physical examinations and those performed at all other visits are symptom-based and TB symptoms are discussed.

h. Subjects with negative QuantiFERON-TB Gold In-Tube test within 35 days of Screening will not require a repeat test, if documentation is available. Subjects with a negative QuantiFERON-TB Gold In-Tube test during the Screening Period will have repeated QuantiFERON-TB Gold In-Tube test at Weeks 2, 4, 6, 8, 12, 16, 20, and 26/PD, unless the Investigator has decided to initiate TB prophylaxis in that subject. For subjects with an indeterminate result during the Screening period, a repeat Screening period test should be performed unless the Investigator decides to initiate TB prophylaxis. If the repeat testing result during the Screening period is negative the QuantiFERON-TB Gold In-Tube test result is considered negative, but if the repeat testing result is indeterminate or positive TB prophylaxis should be initiated at least 3 weeks before Baseline.

   Subjects who have a negative QuantiFERON-TB Gold In-Tube test result during Screening and later develop a positive result will be withdrawn from the study. Subjects who have a negative QuantiFERON-TB Gold In-Tube test result during Screening and later develop an indeterminate result will have repeat testing and will be withdrawn from the study if the repeat testing confirms indeterminate or positive results.

i. Chest x-ray includes posterior-anterior (PA) and lateral views. Subjects with a normal (or one with non-clinically significant findings) CXR within 35 days of Screening would not require a repeat CXR, if documentation is available. All subjects will have repeated CXRs performed to evaluate for TB during the study at Weeks 8, 16, and 26/Premature Discontinuation. A chest CT scan may be used instead of the CXR at investigator discretion. If CXR or chest CT scan was obtained within 4 weeks of Premature Discontinuation, a repeat CXR/chest CT scan is not required.

j. If during Screening the subject has positive QuantiFERON-TB Gold In-Tube test or signs of latent TB in the CXR (or chest CT scan), subject will start and continue at least a 21-day course of TB prophylaxis treatment prior to Baseline (Week 0). Use of TB prophylaxis in subjects with negative TB screening is permitted if warranted based on the opinion of the investigator, but must be started during Screening in this case (i.e., TB prophylaxis should not be initiated after randomization). Subjects who initiate TB prophylaxis should continue the prophylaxis regimen for the duration of the subject's participation in the study (up to the 70 day follow call). Subjects with signs of active TB are excluded from trial participation.

k. Subjects with a normal (or one with non-clinically significant findings) ECG within 90 days of Screening would not require a repeat ECG, if documentation is available.

l. Dipstick urinalysis will be completed by the central laboratory 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.

Table 1. Study Activities (Continued)

m. Serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy test will be performed at Baseline (Week 0) Visit, and the Week 26/Premature Discontinuation Visit for all women of childbearing potential. The frequency can be increased up to every visit as per local regulations. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

n. 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. For subjects who are negative for HBs Ag but are positive for core antibodies (HBc Ab Total), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary. Anti-Hepatitis C will be performed at Screening and will be exclusionary. All subjects will be tested for HIV-1 and documented that the test has been performed. This testing is to be done at a central laboratory. A subject will not be eligible for study participation if confirmatory testing for anti-HIV-1 antibody is positive. AbbVie will not receive results from the testing and not be made aware of any positive result. If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors. If the subject had negative HBV and Anti-Hepatitis C test results from the central lab, these tests will not be required to be repeated if the results were obtained within 35 days of the re-screening visit.

o. Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) performed if ANA result is positive.

p. Blood samples for the measurement of adalimumab and anti-adalimumab antibody (AAA) concentrations will be collected prior to dosing. If the subject Prematurely Discontinues, blood samples for the measurement of adalimumab and AAA concentrations will be collected.

q. Blood samples for the measurement of adalimumab and anti-adalimumab antibody (AAA) concentrations will be collected prior to dosing ONLY if the subject qualifies for dose escalation.

r. Pharmacogenetic and Biomarker mRNA samples are optional. A separate consent must be signed prior to the sample draw.

s. Samples are to be obtained if subject discontinues the study at or after Week 8.

t. Subject will begin mandatory corticosteroid taper at Week 4. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, he/she must be withdrawn from the study.

u. Collection of Serious Adverse Events (SAEs) and protocol-related nonserious adverse events begins the day the subject signs the informed consent. Collection of AEs begins on Day –7 for subjects who initiate TB prophylaxis.

v. Administration of drug should be performed after all assessments and examinations scheduled for that day have been completed as much as possible. Starting at or after Week 12 and if the subject qualifies for dose escalation (criteria defined in Section 5.3.1.1 and per investigator discretion), the subject may receive 80 mg of adalimumab eow.

w. Dosing may occur onsite by appropriate site staff or the subject or their qualified designee can administer doses when not at the site.

x. For damaged or replacement study drug, subject should stay on their dosing schedule established by the Baseline (Week 0) visit.

y. Procedure should be performed if subject doses onsite, if subject doses at home these procedures are not required.

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 AE information (discussed in Section 6.1.4). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

At the Screening visit, the subject will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria at all Screening Visits and at the Baseline (Week 0) Visit.

Medical and Surgical History

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

A complete medical and surgical history, history of tobacco and alcohol use, will be obtained from each subject during the Screening Period. An updated medical history will be obtained at the Baseline (Week 0) Visit to ensure that the subject still qualifies.

Physical Examination

A physical exam will be performed at the designated study visits in Table 1. A count of the number of cutaneous fistulas draining upon gentle compression must be performed during each physical exam. Fistulas will be classified as abdominal or perianal/anal.

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

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, body weight (should be obtained without shoes), and body temperature will be obtained at the designated study visits in Table 1. Blood pressure, pulse rate and respiratory rate should be performed before blood draws are performed. Height will be measured at the Screening Visit only (with shoes off, and then adding 1 inch or 2.5 cm for CDAI calculation). All measurements will be recorded in metric units if possible.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at the designated study visits in Table 1. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. 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 clinical research associate (CRA) and kept with subject's source documents onsite.

For subjects with a normal (or one with non-clinically significant findings) 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 SDP 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.

Chest X-Ray (CXR)

All subjects 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 (or one with non-clinically significant findings) CXR within 35 days of Screening, provided all protocol required documentation is available at the site (as outlined below).

Chest computerized tomography (CT) scan may be substituted for CXR if warranted based upon the opinion of the investigator.

All subjects will have repeat CXRs performed to evaluate for TB during the study at Weeks 8, 16, and 26/Premature Discontinuation. If CXR or chest CT scan was obtained within 4 weeks of Premature Discontinuation, a repeat CXR/chest CT scan is not required.

In the assessment of CXR/chest CT scan, a **radiologist** must note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB as well as the presence of hilar and/or mediastinal lymphadenopathy. In the assessment of the CXR or chest CT scans at Weeks 8, 16, and 26/PD, a radiologist must compare the results to the Screening image and note the presence of the above factors as well as the presence of hilar and/or mediastinal lymphadenopathy. The Principal Investigator (or designee) will indicate the clinical significance of any findings and will sign and date the report.

TB Screening

All subjects should be screened for latent TB infection (LTBI), including those with a prior history of BCG administration.

LTBI screening consists of:

- QuantiFERON-TB Gold In-Tube test (QTF),
- CXR (or chest CT, at the Investigator's [or designee] discretion),
- Medical history of contact with active TB.

During Screening Period:

If any one of the three assessments (QTF, CXR/CT or medical history) is positive, the subject will be considered to have LTBI and will receive TB prophylaxis.

For subjects with an indeterminate QTF result during the Screening period, a repeat Screening period test should be performed with another blood or the subject must initiate TB prophylaxis prior to enrolling in the study. If the repeat testing result during the Screening period is negative the QTF test result is considered negative, but if the repeat testing result is indeterminate or positive TB prophylaxis should be initiated.

In the assessment of the Screening period CXR/chest CT scan, a radiologist must note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB as well as the presence of hilar and/or mediastinal lymphadenopathy. The Principal Investigator must indicate the clinical significance of any findings and contact the AbbVie SDP to discuss any clinically significant abnormal findings before enrolling the subject. The Principal Investigator (or designee) will sign and date each report.

Subjects who have a diagnosis of LTBI during Screening and do not initiate prophylaxis cannot be enrolled.

Subjects who have a diagnosis of LTBI and agree to initiate prophylaxis should be consulted with a TB specialist (a physician with TB treatment knowledge and experience) regarding the selection of the appropriate TB prophylaxis regimen as per Centers for Disease Control (CDC) recommendations or local guidelines.

Initiation of TB prophylaxis in subjects with negative LTBI screening is permitted during the Screening period as warranted based on the opinion of the investigator.

Subjects with an LBTI diagnosis or those in whom TB prophylaxis is electively initiated will receive TB prophylaxis for at least 21 days (before or on the Day –21 visit) prior to Baseline (Week 0), and are required to have a Day –21 and Day –7 visits. At Day –21,

the CDAI and hs-CRP must be obtained and must meet the entry criteria in Section 5.2. For the calculation of the CDAI on Day –21, the hematocrit value obtained at the first screening visit will be used. After initiation of TB prophylaxis, subjects will return to the clinical site 7 days (at Day –7) prior to Baseline (Week 0) to have safety labs drawn, including hs-CRP. The hematocrit and hs-CRP values obtained at Day –7 will be used to calculate the Baseline (Week 0) CDAI to confirm eligibility for study enrollment.

All subjects who initiate TB prophylaxis should continue the prophylaxis regimen for the duration of the subject's participation in the study, including the 70-day follow-up period. TB prophylaxis may only be initiated during the Screening period and is not permitted to be initiated during the study. If the Investigator feels initiation of TB prophylaxis is warranted after the subject has been randomized, the subject must be withdrawn from the study.

Prophylactic treatment for TB should be captured on the concomitant medications page in the eCRF and in the source documents. Prior therapy should be captured in medical history.

After Week 0:

All subjects will be monitored for signs and symptoms suggestive of active TB at all visits.

Subjects who initiate TB prophylaxis should continue the prophylaxis regimen for the duration of the subject's participation in the study and the study follow-up period. These subjects will not require repeat QTF testing but will undergo repeat chest imaging at Weeks 8, 16, and 26/Premature Discontinuation.

Subjects who are negative for LTBI during screening and are not taking TB prophylaxis will have their QTF repeated at Weeks 2, 4, 6, 8, 12, 16, 20, and 26/Premature Discontinuation and the chest imaging repeated at Weeks 8, 16, and 26/Premature Discontinuation.

In the assessment of the CXR or chest CT scans at Weeks 8, 16, and 26/PD, a radiologist must compare the results to the Screening image and note the presence of the following factors 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB, as well as the presence of hilar and/or mediastinal lymphadenopathy. The Principal Investigator must indicate the clinical significance of any findings and contact the AbbVie SDP to discuss any clinically significant abnormal findings and determine the next steps. The Principal Investigator (or designee) will sign and date each report.

Subjects who have a negative QTF test result during Screening and later develop a positive QuantiFERON-TB Gold In-Tube test result will be withdrawn from the study.

Subjects who have a negative QTF test result during Screening and later develop an indeterminate result will have repeat testing and will be withdrawn from the study if the repeat testing result is indeterminate or positive.

TB prophylaxis is not permitted to be initiated during the study.

For subjects who develop signs and symptoms suggestive of active TB or with negative TB Screening who are withdrawn later from the study due to a positive/indeterminate QuantiFERON-TB Gold In-Tube test result or CXR/chest CT findings, a TB specialist (a physician with TB treatment knowledge and experience) should be consulted regarding appropriate patient management.

Table 2. Chart for TB Assessments at Screening and After Week 0

Screening Period				After Week 0	
				Monitoring For:	
QTF	CXR/CT	Medical History	TB Prophylaxis Required	LTBI	Active TB
+	+	+	Yes	No	Yes^
+	+	-	Yes	No	Yes^
+	-	+	Yes	No	Yes^
+	-	-	Yes	No	Yes^
-	+	+	Yes	No	Yes^
-	-	+	Yes	No	Yes^
-	+	-	Yes	No	Yes^
-	-	-	No	Yes*	Yes^

* During follow-up, subjects who are negative for LTBI during screening and are not taking TB prophylaxis will have their QTF repeated at Weeks 2, 4, 6, 8, 12, 16, 20, and 26/Premature Discontinuation and the chest imaging repeated at Weeks 8, 16, and 26/Premature Discontinuation. Subjects who are negative for LBTI during Screening who initiate TB prophylaxis per the Investigator's discretion do not require repeat QTF testing.

^ All subjects will be monitored for signs and symptoms suggestive of active TB at all visits. CXR (or chest CT, at the Investigator's [or designee's] discretion) will be repeated Weeks 8, 16, and 26/Premature Discontinuation. If there are signs or symptoms suggestive of active TB, and/or changes in the chest imaging, a diagnostic investigation must be done.

Physician TB Evaluation

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 the designated study visits in Table 1. For any subject with clinical signs/symptoms of active TB or newly identified TB risk factors, a CXR/chest CT scan (per investigator discretion) may be required for evaluation of active TB, and it is recommended to contact the SDP for further guidance. Subjects with confirmed active TB must be discontinued from the study and receive standard of care based on consultation with a local TB specialist (a physician with TB treatment knowledge and experience).

Patient Reported Outcomes and Questionnaires

- IBDQ – Inflammatory Bowel disease Questionnaire (IBDQ) will be completed at the time points indicated in (Appendix G).

Crohn's Disease Activity Index (CDAI)

A CDAI will be calculated from a subject diary, physical exam, and appropriate laboratory values at the designated study visits in Table 1.

Beginning with the Day –21 Visit (in case subject initiates TB prophylaxis) or Baseline (Week 0) evaluation through Week 26 including unscheduled visits, the CDAI will be calculated using a hematocrit value from the preceding visit's laboratory work.

CDAI at Visit	HCT Value Utilized
Screening Day –21	Original Screening Visit (Up to Day –35)
Baseline (Week 0)	Original Screening Visit/Screening Day –7
Week 2	Week 0
Week 4	Week 2
Week 6*	Week 4
Week 8*	Week 6
Week 10*	Week 8
Week 12*	Week 8 or unscheduled visit if more recent
Week 14*	Week 12
Week 16*	Week 12 or unscheduled visit if more recent
Week 18*	Week 16
Week 20*	Week 16 or unscheduled visit if more recent
Week 22*	Week 20
Week 24*	Week 20 or unscheduled visit if more recent
Week 26	Week 20 or unscheduled visit if more recent

* When evaluating any subject on open-label adalimumab 40 mg eow who are being considered for dose escalation for **inadequate response**, the hematocrit value used to determine the CDAI should be obtained at the previous visit where blood samples were collected for hematology and chemistry whether it is a scheduled or unscheduled blood draw or visit.

For the CDAI questions regarding presence of anal fistulas and other fistulas, all fistulas detectable on physical examination (draining and non-draining) should be captured and noted for calculation of the CDAI.

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

For question seven (7), hematocrit results from central laboratory will be used for the CDAI calculation. If the hematocrit value contains more than one decimal point, the rounding will be allowed to the tenths decimal (e.g., Hct value 33.44 will be captured as 33.4, Hct value of 33.45 will be captured as 33.5). The Hct values either prior to completing the calculation or at the subtotal box 7 of the CDAI should not be rounded to a whole number.

The height obtained at Screening should be used when selecting the standard weight in Appendix D, and this standard weight should be used for calculating every CDAI throughout subject participation in the study.

Standard height is calculated by using the height obtained at Screening (without shoes) plus one inch or 2.5 cm.

Body weight should be captured without shoes. If the body weight that obtained at the time of assessment is not captured in kilograms (kg), then when converting into kgs, rounding should occur using the second digit after the decimal (also known as the hundredth place) where if the number is 0 – 4 then keep the first digit after the decimal (also known as the tenth place) unchanged. If the second digit after the decimal is 5 – 9 then round up the first digit after the decimal (e.g., 90.246 would be captured as 90.2, 97.687 would be captured as 97.7).

The subtotal of box 8 should not be rounded to a whole number.

The calculation of the CDAI is outlined in Appendix C.

Corticosteroid Taper

At Week 4, all subjects who are on oral steroids will have their dose tapered according to the following schedule:

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

The steroid taper is mandatory and deviations from the taper (or increases in steroid doses) are not permitted. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the subject must be withdrawn from the study. From If a subject who has tapered their corticosteroid dose is judged by the Investigator to have an inadequate response per the PI's judgment, dose escalation (allowed at or after Week 12) should be considered if the subject meets the dose escalation criteria (Section 5.3.1.1), otherwise, the subject should be withdrawn from the study.

Adverse Event

Adverse events will be assessed at every study visit from Day –7 (if the subject initiates TB prophylaxis) or from Baseline (Week 0) through the final study visit (Week 26 or Premature Discontinuation visit for those who prematurely discontinue from the double-blind or OL periods of the study) and at the 70-day follow-up phone call.

Serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study specific informed consent.

Subjects who complete Week 26 or those who prematurely discontinue the study early, 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. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation. Refer to Section 6.0 for additional information.

Subject Diary

Subjects will be dispensed a diary 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 Week 26/PD visit.

If the subject chooses to dose at home, their 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 into the eCRF. 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.

Study Drug Dispensing/Administration

Study drug will be administered to all subjects onsite by site medical staff during all the visits from Baseline (Week 0) through Week 24. No study drug will be administered at Week 26. Detailed instructions and training for the administration of adalimumab are provided in Appendix E and Appendix F. Study drug kits are assigned by IRT following the subjects randomized treatment schedule. If the subject chooses to dose outside of the clinic at the visit weeks specified in Table 1, adalimumab injections occurring during study visits will be performed at the visit by the subject or their designated family member, friend or Healthcare Professional under the supervision of trained medical personnel to reinforce proper aseptic SC injection technique. Subjects or a trained designated family member, friend or Healthcare Professional will perform the injections of adalimumab in the subject's home during the weeks they are not in for scheduled clinic visits.

When dosing onsite, each subject will have a Dosing Log or accountability form at Baseline (Week 0); this log must be filled out each time a dose is administered. In the dosing log, the date and time study drug is administered, and the dose administered will be recorded. Additionally, any discernible departure from the protocol regarding study

drug administration will be recorded on the source documents and on the appropriate drug accountability form.

Site medical staff or subjects, if dosing occurs at the subject's home, 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 (Week 0) Visit date. A ± 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 ± 3 day window, please contact the AbbVie SDP for additional instructions.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and initiate appropriate therapy. When dosing at home subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction. If subjects are unable to reach their study site or experience life-threatening symptoms, they will be instructed to call an emergency number or proceed to the nearest emergency room and then inform the site as soon as possible.

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

Dose Escalation

At or after Week 12, if any subject experiences inadequate response (defined below), the subject may increase dose to open-label adalimumab 80 mg eow. If the subject has received open-label 80 mg eow therapy and continues to demonstrate inadequate response, they should be withdrawn from the study.

For the Purposes of Dose Escalation, Inadequate Response:

Crohn's disease activity index (CDAI) ≥ 200 and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L.

The hs-CRP results used to determine inadequate response should be the most recent available results. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation. The most recent hs-CRP value should first be compared to the most recent CDAI from the previous visit. Then the most recent hs-CRP value should be assessed in relation to CDAI calculated at the current visit. Dose changes are to only occur in accordance with the eow dosing schedule.

For example:

Week 12 CDAI was 190 and the hs-CRP obtained at Week 12 visit was 7 mg/L. The subject returns 2 weeks later and the CDAI at Week 14 is 220. The hs-CRP obtained at Week 12 should first be assessed with the Week 12 CDAI to determine if the inadequate response criteria have been met; which in this case does not meet criteria for dose escalation. Then the hs-CRP obtained at Week 12 should be assessed with Week 14 CDAI, which does meet the criteria for dose escalation; because the latter assessment met the criteria, the subject is eligible for dose escalation.

Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 3 at the visits described in Table 1. Blood draws should be performed after all clinical assessments and questionnaires (CDAI, IBDQ), vital sign determinations are obtained and before study drug administration during a visit, whenever possible.

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.

Table 3. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis	Other	Pregnancy Test
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity Ketones pH Protein Blood Glucose	hs-CRP C. *difficile* toxin Fecal calprotectin Antinuclear antibody (ANA) Anti-double-stranded DNA (anti-dsDNA) – *if ANA positive* HBs Ag HBs Ab HBe Ag HBe Ab HBc Ab Total PCR DNA (if needed) Pharmacokinetic HACA Infliximab Pharmacogenetic (optional) mRNA (optional) HCV HIV (testing to be conducted at central lab) QuantiFERON-TB Gold In-Tube	Serum HCG Urine (testing to be performed locally by designated study personnel)

Hepatitis and HIV Testing

All subjects will be tested for the presence of the HBV at Screening. A positive result for the HBs Ag will be exclusionary. If HBc Ab test results are positive, polymerase chain reaction (PCR) DNA will be performed to exclude the HBV infection, any result that

meets or exceeds detection sensitivity will be exclusionary. If HBe Ag or HBe Ab are positive, the subject's eligibility is per investigator's discretion.

Anti-Hepatitis C antibody will be performed at Screening only. A positive result will be exclusionary.

Subjects will be tested for antibodies to HIV-1 at Screening. This testing is to be done at a central laboratory. A subject will not be eligible for study participation if confirmatory testing for anti-HIV-1 antibody is positive. AbbVie will not receive results from the testing and not be made aware of any positive result. If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors.

If the subject had negative HBV and Anti-Hepatitis C test results from the central lab, these tests will not be required to be repeated if the results were obtained within 35 days of the re-screening visit.

Pregnancy Tests

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. At the Baseline Visit (Week 0) and Week 26/PD subjects 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.

All women of childbearing potential will have a repeat urine pregnancy test at the final onsite Study Visit performed locally by designated study personnel.

Urinalysis

Urine samples will be obtained and sent to the central laboratory for the tests listed in Table 3 at the visits described in Table 1. Microscopic urinalysis will only be performed

d by the central laboratory if the dipstick urinalysis results are abnormal, where abnormal is defined as a ketone, protein, blood value greater than negative or glucose value of greater than a normal.

Other Laboratory Assessments

ANA/anti-dsDNA

Blood samples for antinuclear antibody (ANA) will be obtained per Table 1. Anti-double-stranded DNA (anti-dsDNA) assessments will be performed if ANA is positive.

In the event that subject develops lupus-like symptoms during the study, an additional ANA sample will be obtained.

hs-CRP

Blood samples for hs-CRP will be obtained per Table 1. The site will receive the notification from the central laboratory for the Screening Period. Results obtained during the Day –7 Screening visit (for a subject who started TB prophylaxis) will be used for entry criteria.

The hs-CRP results from Week 2 through Week 8 will remain blinded to Investigator, study site personnel and the subject. The AbbVie safety team will not be blinded to these results. Since investigators are blinded to hs-CRP, the SDP will notify the investigator of an elevated hs-CRP result (> 100 mg/L) and request follow-up.

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

Fecal Calprotectin

Fecal calprotectin will be performed for all subjects as indicated in Table 1 and collection should be performed before study drug administration during a visit as much as possible.

If subjects are unable to provide a sample at the site visit, they will be sent home with a stool sample collection supplies and instructions to assist the subjects with the collection procedures.

The fecal calprotectin results will remain blinded to Investigator, study site personnel and the subject up to and including Week 8.

The central laboratory will be utilized to process and provide results for these laboratory tests.

C. *Difficile* Stool Testing

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

Subjects who are positive for C. *difficile* toxin may be treated appropriately and re-screened.

Pharmacokinetics

Blood samples for adalimumab and anti-adalimumab (AAA) will be collected starting at Baseline (Week 0). Time points are indicated in Table 1.

Blood samples for Infliximab and Human Anti-Chimeric Antibody (HACA) will be collected at Baseline (Week 0).

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected at the time points indicated in Table 1 from each subject who consents to provide samples for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Instructions for the preparation and shipment of pharmacogenetic samples will be provided in the lab manual. Samples will be shipped frozen to the central laboratory in China and then to an AbbVie designated laboratory in China for long-term storage. Samples should not be allowed to thaw prior to arrival at the designated laboratory. Arrangements will be made with the central laboratory for the shipment of PG samples to the specified lab for testing in China.

Samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on adalimumab (or drugs of this class) continues but no longer than 10 years.

5.3.1.3 Blood Samples for Biomarkers Analysis

Collection of Samples for mRNA Assays

One 2.5 mL blood samples for mRNA will be collected at the time points indicated in Table 1 from each subject who consents to provide samples for mRNA analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Instructions for the preparation and shipment of biomarker samples will be provided in the lab manual. Samples will be shipped frozen to the central laboratory in China and then to an AbbVie designated laboratory in China for long-term storage. Samples should not be allowed to thaw prior to arrival at the designated laboratory. Arrangements will be made with the central laboratory for the shipment of mRNA samples to the specified lab for testing in China.

Samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on adalimumab (or drugs of this class) continues but no longer than 10 years.

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.

Collection of Samples for Adalimumab and AAA Assays

Blood samples for adalimumab and AAA assays will be collected by venipuncture into appropriately labeled 4 mL evacuated serum collection tubes (one tube for adalimumab and one tube for AAA) without gel separator immediately prior to dosing. Sufficient blood will be collected to provide approximately 2 mL serum for adalimumab assay and 2 mL serum for AAA assay. Blood will be allowed to clot for 30 – 60 minutes at room temperature before centrifugation.

A maximum of 9 samples are planned to be collected per subject for adalimumab (5 samples) and AAA (4 samples) assays if the subject does not dose escalate. If the subject dose escalates, a maximum of 11 samples are planned to be collected per subject for adalimumab (6 samples) and AAA (5 samples) assays. If all subjects dose escalate, the total number of samples planned will not exceed 1200 (6 samples × 200 subjects) for the adalimumab assay and 1000 (5 samples × 200 subjects) for the AAA assay for the entire study.

Collection of Samples for Infliximab and HACA Assays

Blood samples for infliximab and HACA assay will be collected at Week 0 (Baseline) by venipuncture into appropriately labeled 4 mL evacuated serum collection tube without gel separator at Baseline (Week 0). The sample will be obtained immediately prior to dosing. Blood will be allowed to clot for 30 – 60 minutes at room temperature before

centrifugation. Sufficient blood will be collected to provide approximately two 1 mL serum specimens (one tube for infliximab and one tube for HACA).

The total number of samples planned will not exceed 400 (2 samples × 200 subjects) for the entire study.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab, AAA, infliximab, and HACA assay will be labeled with information such as the following: the type of sample, the study drug number, protocol number, subject number, study week/visit name, and assay type (pharmacokinetic [PK]-Adalimumab or AAA; PK-Infliximab or HACA).

Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory.

Handling/Processing of Adalimumab and AAA Assays

The blood samples for adalimumab and AAA assay will be centrifuged at 1100 – 1600 × g for 10 – 15 minutes within 30 – 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with information such as the following: the study drug name, protocol number, subject number, study week/visit name, and assay type (Pharmacokinetics [PK] Adalimumab or AAA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder freezer 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.

Samples will be shipped frozen from the sites to the designated laboratory in China for testing and storage. Samples should not be allowed to thaw prior to arrival at the designated laboratory.

Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory/AbbVie.

Handling/Processing of Infliximab and HACA Assays

The blood samples for Infliximab and HACA assay will be centrifuged at 1100 – 1600 × g for 10 – 15 minutes within 30 – 60 minutes of collection to separate the serum. The serum samples will be transferred using plastic pipettes into screw-capped polypropylene vials labeled with information such as the following: the study drug number, protocol number, subject number, study week/visit name, and assay type (Infliximab or HACA). The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder freezer 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.

Samples will be shipped frozen to the designated laboratory in China for testing and storage. Samples should not be allowed to thaw prior to arrival at the designated laboratory.

Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory/AbbVie.

5.3.2.3 Disposition of Samples

Frozen serum samples will be packed in dry ice (pellet form) sufficient to last 3 days during transport. Samples will be shipped pursuant to instructions from the onsite CRA. An inventory of the samples will be included in the package for shipment. Arrangements will be made with the central lab for the transfer of samples.

5.3.2.4 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The primary efficacy variable is the proportion of subjects who achieve clinical remission (CDAI < 150) at Week 4.

5.3.3.2 Secondary Variables

The Week 26 efficacy endpoint is proportion of subjects who achieve clinical remission at Week 26 (CDAI < 150) in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

Key secondary efficacy endpoints include:

- Proportion of subjects who achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 4.
- Proportion of subjects who achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who achieved decrease in CDAI ≥ 70 points from Baseline plus at least 30% reduction in hs-CRP from Baseline at Week 8.
- Proportion of subjects who discontinue corticosteroid use and achieve clinical remission (CDAI < 150) at Week 26 in subjects who were taking steroids at Baseline and who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.
- Proportion of subjects who discontinue corticosteroid use and achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who were taking steroids at Baseline and who achieved decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 8.
- Proportion of subjects who achieve clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 4.
- Proportion of subjects who achieve decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 4.

- Proportion of subjects who achieve CDAI < 150 and hs-CRP < 3 mg/L at Week 4.
- Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.
- Proportion of subjects who achieve IBDQ remission (IBDQ ≥ 170 points) at Week 4.
- Proportion of subjects who achieve IBDQ remission at Week 26 in subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.
- Change from Baseline in fecal calprotectin level at Week 4.
- Proportion of subjects who achieve CDAI <150, hs-CRP < 3 mg/L and fecal calprotectin < 250 µg/g at Week 4.
- Proportion of subjects who achieve CDAI <150, hs-CRP < 3 mg/L and fecal calprotectin < 250 µg/g at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

Additional secondary endpoints include:

- Proportion of subjects with clinical remission (CDAI < 150) over time.
- Proportion of subjects with CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline over time.
- Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) over time.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline over time.
- Change from Baseline in CDAI over time.
- Change from Baseline in hs-CRP level over time.
- Change from Baseline in fecal calprotectin level over time.

5.3.4 Safety Variables

Safety analyses will be performed on all subjects who receive at least one dose of study drug. Incidence of adverse events, changes in vital signs, physical examination results, and clinical laboratory data will be assessed.

5.3.5 Pharmacokinetic Variables

Serum adalimumab concentrations will be determined from samples collected just prior to dosing at Baseline (Week 0), Week 4, Week 8, Week 12, and Week 26/Premature Discontinuation. Blood samples for the measurement of serum adalimumab concentrations at Week 14, Week 16, Week 18, Week 20, Week 22 and Week 24 will be collected prior to dosing only if the subject qualifies for dose escalation.

Serum anti-adalimumab antibody (AAA) will be determined from the samples collected just prior to dosing at Baseline (Week 0), Week 4, Week 12 and Week 26/Premature Discontinuation. Blood samples for the measurement of serum AAA at Week 14, Week 16, Week 18, Week 20, Week 22 and Week 24 will be collected prior to dosing only if the subject qualifies for dose escalation.

Blood samples will also be collected for measurement of infliximab serum levels and HACA just prior to dosing at Baseline (Week 0).

5.3.6 Pharmacogenetic Variables

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or the subject's response to adalimumab, or other study treatment, 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 believed to be related to the disease (examples include but are not limited to LCN2, CCL20, NOD2) or drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to adalimumab, drugs of this class, or the disease. The samples may also

be used for the development of diagnostic tests related to adalimumab, drugs of this class, or disease. The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.7 mRNA Variables

Samples from subjects may be analyzed for mRNA expression levels contributing to the subject's response to disease or study treatment, in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Messenger RNA levels related to disease or response to drug therapy will be measured in peripheral whole blood. For analysis, mRNA expression may be analyzed using a microarray and polymerase chain reaction (PCR) technique in peripheral blood samples. This analysis will measure the levels of essentially all mRNAs present in the collected peripheral blood samples. Messenger RNA analysis will be limited to studying response to Crohn's disease; no other analyses will be performed. Results of biomarker mRNA are considered exploratory and may not be included in 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 SDP.
- 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 would place the subject at risk as determined by the AbbVie SDP (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 SDP.
- Subject is non-compliant with TB prophylaxis.
- Subjects with negative TB Screening before Week 0 who later develop a positive/indeterminate QuantiFERON-TB Gold In-Tube test result or CXR/chest CT findings.
- The subject becomes pregnant while on study drug.
- Subject has dysplasia 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 SDP.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Premature Discontinuation 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. The information will be recorded on the appropriate eCRF page. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

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

Study drug will be provided as a sterile solution for SC injection, contained in pre-filled syringes containing adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. The investigator or designee will subcutaneously administer study drug to the subject per the dosing schedule.

Double-Blind Period (Week 0 – Week 8)

Adalimumab 40 mg/0.8 mL or Placebo for Adalimumab 0.8 mL:

During the randomized double-blind treatment period, subjects will be randomized to one of two groups. Subjects randomized to adalimumab will receive blinded adalimumab

160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and Week 6. Subjects randomized to placebo will receive matching placebo at Week 0 and Week 2, adalimumab 160 mg at Week 4, and adalimumab 80 mg at Week 6. At Week 8, all subjects will commence and 18-week OL period during which they will receive adalimumab 40 mg eow.

Open-Label Period (Week 8 – Week 26)

Adalimumab 40 mg/0.8 mL:

Starting at the Week 8 visit all subjects will receive one injection with 40 mg adalimumab and then eow until Week 26. If subject qualifies for dose escalation during the OL Period the subject may escalate to adalimumab 80 mg eow.

The duration of the study could be up to 39 weeks which includes a Screening Period of up to 35 days, 8 weeks double-blind treatment periods, an 18-week OL period, and a follow-up period 70 days from the last dose of study drug to obtain information on any new or ongoing AEs.

At or after Week 12, any subject who experiences inadequate response (defined below), may increase dose to open-label adalimumab 80 mg eow. If the subject has received open-label 80 mg eow therapy and continues to demonstrate inadequate response, they should be withdrawn from the study.

No dose will be given at the final visit (Week 26).

<u>For the Purposes of Dose Escalation, Inadequate Response:</u>

Crohn's disease activity index (CDAI) ≥ 200 and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L.

The hs-CRP results used to determine inadequate response should be the most recent available results. Assessment of inadequate response should include consideration by

the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation. The most recent hs-CRP value should first be compared to the most recent CDAI from the previous visit. Then the most recent hs-CRP value should be assessed in relation to CDAI calculated at the current visit. Dose changes are to only occur in accordance with the eow dosing schedule.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 4.

Table 4. Study Drugs

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Pre-filled syringe	40 mg/0.8 mL solution for injection 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	Parenteral	Pre-filled syringe	0.8 mL solution for injection mannitol, Citric Acid monohydrate, Sodium citrate, Disodium phosphate dehydrate, Sodium dihydrogen phosphate dehydrate, Sodium chloride, Polysorbate 80, water for injections, Sodium Hydroxide added as necessary to adjust pH	AbbVie

5.5.2.1 Packaging and Labeling

Investigational product will be packaged separately in 0.8 mL syringe containing either adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. Each dosing kit carton contains two pre-filled syringes to accommodate study design. The syringe and/or carton labels will minimally contain the information as required per country 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 drug supplies are provided in Appendix E and Appendix F.

5.5.2.2 Storage and Disposition of Study Drug

Adalimumab pre-filled syringes are to be stored protected from light at 2° to 8°C/36° 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 (daily is recommended) 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), if applicable, deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

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

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique identification number by the IRT system at the screening study visit. Subjects who meet the entry criteria in Section 5.2.1 and Section 5.2.2 will proceed to be enrolled into the study. Subjects who enter the study will be randomized at Baseline (Week 0) in a 1:1 ratio to receive adalimumab or placebo. The randomization will be stratified by Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline (Week 0) and corticosteroid use at Baseline.

The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IRT. Before the study is initiated, the access information for the IRT

system will be provided to each site. Study drug will be administered at the study visits summarized in Table 1.

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 or miss their regularly scheduled visit for the injection of study medication on their regularly scheduled dosing date, they should return to the site to take the forgotten or missed 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.

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 remain full at the study site. The subject should resume their regular dosing schedule based on the first dosing date at Baseline (Week 0) and the site should obtain new study drug kit assignment from the IRT system.

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 Interactive Response Technology (IRT) 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 SDP (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.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

If the subject doses at home, the subject or their qualified designee will administer all doses of assigned 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 diary 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 return the diary, 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 diary 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, 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 in the IRT system including date received, the lot number, box number(s), date dispensed, subject

number, drug expiration date, and the identification with date of the person dispensing the drug. All expired drug will be removed from refrigerated storage and placed under quarantine until such a time as it can be returned to AbbVie.

All empty Investigational Product (IP) boxes will be inventoried by the site and verified by the Monitor. Monitors and site staff will complete study medication accountability via study medication logs and empty IP at each visit. Once the monitor has verified drug accountability at the site, the site staff and monitor will document that the used pre-filled syringes have been destroyed, using appropriate biohazard precautions. Used Sharps containers should never be opened. After verification of drug accountability by the site staff and the monitor, used pre-filled syringes will be destroyed by the site. A copy of the destruction methodology should be maintained at the site's facility. All unused study drug must be inventoried, accounted for and returned to Depot for destruction. The IRT system will produce list of study drug being returned; the list should be enclosed with the shipment.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The study design was chosen to demonstrate the efficacy of adalimumab as induction and maintenance therapy for Crohn's disease. Subjects with active CD who meet all inclusion criteria and none of the exclusion criteria are eligible for this study. The specific subject population chosen was based on the unmet medical need for subjects with moderately to severely active symptoms plus evidence of active inflammation (as documented by hs-CRP).

The first 4 weeks of the double-blinded period will evaluate the efficacy of adalimumab (160/80 mg at Week 0/2) to induce clinical remission (CDAI < 150) at Week 4 compared to placebo. Recognizing the severe and debilitating nature of Crohn's disease and the associated suffering experienced by subjects, subjects randomized to placebo will receive induction with adalimumab 160/80 mg at Weeks 4/6 (subjects randomized to adalimumab will receive adalimumab 40 mg at Weeks 4 and 6 with matching placebo to retain

blinding). Beginning at Week 8, all subjects will receive open-label therapy with adalimumab 40 mg every other week. Rates of remission at Week 26 will be evaluated in subjects meeting the definition for response (reduction in CDAI ≥ 70 points from Baseline) after induction therapy (determined at Week 8) and compared against a clinically meaningful remission rate obtained using the data from adult placebo from Western CD Study M02-404 (see Section 8.2 for details).

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

Subjects with active CD who meet all inclusion criteria and none of the exclusion criteria are eligible for this study. The specific subject population chosen was based on the unmet medical need for subjects with moderately to severely active CD in China who also have evidence of active inflammation (by hs-CRP).

5.6.4 Selection of Doses in the Study

The dose of adalimumab to be tested in the Chinese patient population is the same dose approved globally (US, EU, and Japan package labels) for patients with Crohn's disease and was selected based on similar pharmacokinetics in Chinese subjects observed in Study M14-232 as in studies conducted in Western subjects. The 160/80 mg induction dose was associated with the greatest efficacy in Study M02-403 and Study M14-232, and is the approved dose in the US, Japan, and one of the two approved doses in Europe. The 40 mg every other week maintenance dose is the approved dose in the US, EU, and Japan, and the 80 mg every other week dose for subjects with inadequate response is the same dose approved in Japan for subjects with inadequate response to 40 mg every other week maintenance dosing.

6.0 Complaints

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

The investigational product in this trial contains both:

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7. 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 is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An 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, meet protocol specific criteria (See 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 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.

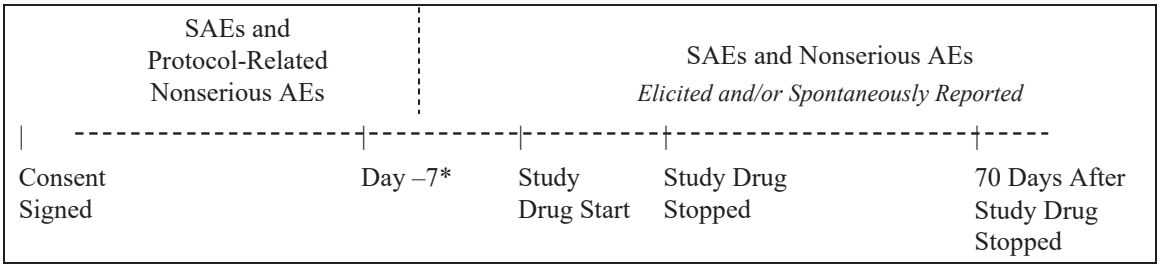
6.1.4 Adverse Event Collection Period

All adverse events reported from the time of Day –7 for subjects initiating TB prophylaxis during the screening period (if applicable) or from the time 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 and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

All subjects who do not initiate adalimumab therapy not supplied in the context of the clinical trial after the end of study participation will have a follow-up phone call 70 days after the last administration of study drug to obtain information on any new or ongoing AEs.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* If the subject initiates TB prophylaxis during the Screening Period, AEs will be collected starting at the Day –7 visit. If the subject does not initiate TB prophylaxis during the Screening Period, AEs will be collected starting at Baseline (SAEs and nonserious protocol related AEs are collected starting at the time of consent).

6.1.5 Adverse Event Reporting

In the event of a SAE, and additionally, any nonserious event of malignancy in subjects 30 years of age or younger, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the event by entering the SAE or nonserious event of malignancy in subjects 30 years of age and younger into the electronic data capture (EDC) system. Serious adverse events

and non-serious events of malignancy in subjects 30 years of age and younger that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

[redacted]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team Hotline

[redacted]

[redacted]

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

[redacted]

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 adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event 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" (see Section 6.1.1 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, device not working properly, or packaging issues.

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

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

6.2.2 Reporting

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

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

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. 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 Clinical Monitors:

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.

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analysis Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab in inducing and maintaining clinical remission in Chinese subjects with moderately to severely active Crohn's disease and elevated hs-CRP.

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) set includes all subjects who are randomized. ITT subjects will be analyzed as randomized. ITT set is the primary population for the efficacy analysis during the double-blind and open-label treatment periods.

The safety set consists of all enrolled subjects who received at least one injection of 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

All statistical tests will be two-tailed with the significance level 0.05. Descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, median, 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).

8.1.3 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics. The p-value will be provided to assess the comparability of the treatment groups assigned by randomization. The continuous variables will be analyzed using the analysis of variance (ANOVA), and discrete variables will be analyzed using the chi-square test or Fisher's exact test.

8.1.4 Statistical Analyses of Efficacy

8.1.4.1 Primary Efficacy Variable

The primary efficacy variable is proportion of subjects who achieve a CDAI < 150 at Week 4.

The comparisons between treatment group difference on the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline (Week 0) and corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between the treatment groups will be calculated. The ITT set will be used for the analysis. Missing CDAI or hs-CRP will be imputed using the non-responder imputation (NRI) approach. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses.

8.1.4.2 Additional Efficacy Variables

The Week 26 efficacy endpoint is proportion of subjects who achieve clinical remission at Week 26 (CDAI < 150) in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8. The one sample Exact test will be performed by comparing it to the clinically meaningful constant rate, and the two-sided 95% CI will be provided.

For key and additional secondary efficacy endpoints, continuous variables will be analyzed using Analysis of Covariance (ANCOVA) model including factor for treatment group, stratification factors and Baseline values. For categorical endpoints with comparison between the treatment groups, the difference in proportions of subjects between treatment groups will be analyzed using the CMH test adjusted for stratification variables. Additionally, the CHM based two-sided 95% confidence interval for the difference in proportions will be provided. For categorical endpoints with comparison to the clinically meaningful constant rate, the one sample Exact test will be performed and

the two-sided 95% CI will be provided. The NRI imputation method will be used for subjects with missing data at the time point evaluated. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The LOCF method will also be used as the sensitivity analyses.

Change from Baseline in continuous endpoints will be analyzed using an ANCOVA model including factors of treatment and adjusting for the baseline values and the stratification variables. For analyses of changes from Baseline variables, both LOCF and observed case analyses will be performed. The LOCF analysis is considered primary for inferential purposes.

8.1.5 Statistical Analyses of Safety

Laboratory data, adverse events (AEs), and vital signs are the primary safety parameters in this study. All safety analyses will be performed using the Safety set, which includes all subjects who enrolled into this study and received at least one dose of study drug. Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 70 days after the last dose of the study drug. An overview of treatment-emergent AEs, including AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 17.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage. Treatment-emergent AEs will be summarized separately for the double-blind dosing period (Week 0 to Week 8) and the OL period (Week 8 to 70 days after the last dose of the study medication).

Changes in laboratory data will be described using statistical characteristics and compared between treatment groups will be performed using a one-way Analysis of Variance (ANOVA). In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

8.1.6 Other Statistical Analyses of Efficacy

The subgroups listed below will be used in subgroup analyses of the primary endpoint.

- Sex (male, female)
- Age (≤ median, > median)
- Baseline fecal calprotectin (≤ median, > median)
- Baseline fecal calprotectin (≤ 250 µg/g, > 250 µg/g)
- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- hs-CRP at Baseline (< 10 and ≥ 10 mg/L)
- hs-CRP at Baseline (< 30 and ≥ 30 mg/L)
- hs-CRP at Baseline (≤ median, > median)
- Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline
- Baseline CDAI (≤ median, > median)
- Weight (≤ median, > median)
- Baseline albumin (≤ median, > median)
- Disease duration (≤ 3 years, > 3 years)
- Disease duration (≤ median, > median)

8.1.7 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized 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. The relationship between adalimumab concentrations and clinical response will be determined as appropriate.

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 AEs may be evaluated.

8.2 Determination of Sample Size

The Week 4 primary efficacy endpoint is defined as the proportion of subjects achieving CDAI < 150. Based on the adalimumab CD clinical trial results, the remission rate was 67% in the ADA 160/80 mg treatment group and 40% in the ADA 80/40 mg treatment group in China Phase 2 CD Study M14-232 (no placebo group in that study), and 40% in the ADA 160/80 mg treatment group and 8% in the placebo group in Western CD Study CLASSIC I (Study M02-403) based on subjects with elevated CRP at baseline (hs-CRP ≥ 3 mg/L). Considering that the placebo effect in China Phase 3 study will potentially be higher than the Western placebo rate, and the treatment effect in the ADA 160/80 mg treatment group will potentially be lower than the China Phase 2 CD study, the assumption of remission rates at Week 4 for this study is 24% and 47% for placebo and the ADA 160/80 mg treatment groups, respectively, with the expected treatment difference of 23%. A sample size of 100 subjects per arm (total 200 subjects) will provide power of 90% to detect the 23% treatment difference in the primary efficacy endpoint between the ADA 160/80 mg treatment group and placebo (1:1 randomization ratio), using two-sided Fisher's exact test at a 0.05 significance level.

If the overall Week 8 response rate is over 50%, it is expected that approximately 100 subjects who are Week 8 responders will enter the open-label maintenance period and comprise the analysis population for Week 26 endpoints. Based on the observed Week 26 remission rate (52% [34/66]) for the ADA 40 mg EOW treatment group in Western CD Study M02-404 in anti-TNF naïve subjects with elevated CRP at baseline (hs-CRP ≥ 3 mg/L) who responded to adalimumab induction therapy, the sample size of 100 subjects will allow ≥ 99% power to detect remission rate at Week 26 of 52% against a clinically meaningful remission rate of 30% using one-sample Exact test at a two-sided 0.05 significance level. The remission rate of 30% was obtained using the upper bound of the 95% CI of the adult placebo rate from the Western CD Study M02-404 in the same subgroup of patients.

Prior to the completion of enrollment, assessment of the sample size based on the blinded data (overall event rate at Week 4) will be conducted.

8.3 Randomization Methods

At Baseline (Week 0), subjects will be randomized 1:1 to double-blinded adalimumab or placebo. The randomization will be stratified by Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline (Week 0) and corticosteroid use at Baseline.

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) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and 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 answer all questions regarding this study. 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, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject 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.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Samples for pharmacogenetic and biomarker analysis will only be collected if the subject has voluntarily signed and dated a separate informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate informed consent must be signed before the pharmacogenetic and biomarker samples are collected and testing is performed. If the subject does not consent to the pharmacogenetic and biomarker analysis, it will not affect the subject's participation in the study.

10.0 Source Documents, Data Collection and Electronic Case Report Forms

10.1 Source Documents

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

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

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. All eCRF data required by this protocol will be recorded by investigative site personnel in 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.

The following assessments will be completed by subjects on paper:

- IBDQ

Site staff will verify completion of these forms. 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 study subject who is making the correction. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry.

The questionnaire administrator will review the questionnaire for completeness and accuracy. The subject-completed questionnaires will be transcribed into the EDC system by study personnel. The completed paper questionnaire will be considered source.

The principal investigator will review the case report forms for completeness and accuracy and sign and date the set of case report forms where indicated. AbbVie

personnel (or their representatives) will review the case report forms periodically for completeness, legibility, and acceptability. AbbVie (or their representatives) will be allowed access to all source documents in order to verify case report form entries.

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 and biomarker research that may be done using DNA/mRNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient 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 and biomarker information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic and biomarker 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 (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

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, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adalimumab for the Induction and Maintenance of Clinical Remission in Chinese Patients with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-reactive Protein
Protocol Date:	19 October 2015

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Hanauer SB, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2001;96(3):635-43.
2. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-17.
3. Probert CS, Jayanthi V, Rampton DS, et al. Epidemiology of inflammatory bowel disease in different ethnic and religious groups: limitations of aetiological clues. Int J Colorectal Dis. 1996;11(1):25-8.
4. Ng SC, Tang W, Ching JY, et al; Asia-Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. Gastroenterology. 2013;145(1):158-65.
5. Zhao J, Ng SC, Lei Y, et al. First prospective, population-based inflammatory bowel disease incidence study in mainland of China: the emergence of "western" disease. Inflamm Bowel Dis. 2013;19(9):1839-45.
6. Zeng Z, Zhu Z, Yang Y, et al. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guandong Province, China: a prospective population-based study. J Gastroenterol Hepatol. 2013;28(7):1148-53.
7. Chinese Cooperative Group for the study on IBD, Chinese Society of Gastroenterology. Ouyang Q, Hu PJ, Qian JM, et al. Consensus on the management of inflammatory bowel disease in China in 2007. J Dig Dis. 2008;9(1):52-62.
8. Zheng JJ, Zhi P, Wang YM, et al. Short-term study of infliximab treatment for Crohn's disease in China. J Dig Dis. 2011;12(2):105-9.

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
[redacted]		Clinical
		Statistics
		Pharmacokinetics/Pharmacodynamics
		Clinical
		Clinical
		Clinical

Appendix C. Crohn's Disease Activity Index (CDAI)

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

Appendix D. Standard Weights

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Adjusted Height* cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
121.9 (48.0)		40.8 (89.9)
123.2 (48.5)		41.3 (91.0)
124.5 (49.0)		41.8 (92.1)
125.7 (49.5)		42.3 (93.3)
127.0 (50.0)		42.8 (94.4)
128.3 (50.5)		43.4 (95.6)
129.5 (51.0)		43.9 (96.8)
130.8 (51.5)		44.4 (98.0)
132.1 (52.0)	55.5 (122.4)	45.0 (99.2)
133.4 (52.5)	55.7 (122.7)	45.5 (100.4)
134.6 (53.0)	55.8 (123.1)	46.1 (101.6)
135.9 (53.5)	56.0 (123.5)	46.6 (102.8)
137.2 (54.0)	56.2 (123.9)	47.2 (104.1)
138.4 (54.5)	56.4 (124.4)	47.8 (105.3)
139.7 (55.0)	56.7 (124.9)	48.3 (106.6)
141.0 (55.5)	56.9 (125.5)	48.9 (107.9)
142.2 (56.0)	57.2 (126.1)	49.5 (109.1)
143.5 (56.5)	57.4 (126.7)	50.1 (110.4)
144.8 (57.0)	57.7 (127.3)	50.7 (111.7)
146.1 (57.5)	58.1 (128.0)	51.3 (113.0)
147.3 (58.0)	58.4 (128.7)	52.2 (115.0)
148.6 (58.5)	58.7 (129.5)	52.6 (116.0)
149.9 (59.0)	59.1 (130.3)	53.1 (117.0)
151.1 (59.5)	59.5 (131.1)	53.6 (118.3)
152.4 (60.0)	59.9 (132.0)	54.2 (119.5)
153.7 (60.5)	60.3 (132.9)	54.8 (120.8)
154.9 (61.0)	60.7 (133.8)	55.3 (122.0)
156.2 (61.5)	61.1 (134.8)	56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Adjusted Height* cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
158.8 (62.5)	62.1 (137.0)	57.4 (126.5)
160.0 (63.0)	62.6 (138.0)	58.0 (128.0)
161.3 (63.5)	63.0 (139.0)	58.7 (129.5)
162.6 (64.0)	63.5 (140.0)	59.4 (131.0)
163.8 (64.5)	64.1 (141.3)	60.1 (132.5)
165.1 (65.0)	64.6 (142.5)	60.8 (134.0)
166.4 (65.5)	65.2 (143.8)	61.4 (135.5)
167.6 (66.0)	65.8 (145.0)	62.1 (137.0)
168.9 (66.5)	66.4 (146.5)	62.8 (138.5)
170.2 (67.0)	67.1 (148.0)	63.5 (140.0)
171.5 (67.5)	67.8 (149.5)	64.2 (141.5)
172.7 (68.0)	68.5 (151.0)	64.9 (143.0)
174.0 (68.5)	69.2 (152.5)	65.5 (144.5)
175.3 (69.0)	69.8 (154.0)	66.2 (146.0)
176.5 (69.5)	70.5 (155.5)	66.9 (147.5)
177.8 (70.0)	71.2 (157.0)	67.6 (149.0)
179.1 (70.5)	71.9 (158.5)	68.3 (150.5)
180.3 (71.0)	72.6 (160.0)	68.9 (152.0)
181.6 (71.5)	73.4 (161.8)	69.6 (153.5)
182.9 (72.0)	74.1 (163.5)	70.3 (155.0)
184.2 (72.5)	75.0 (165.3)	71.2 (156.9
185.4 (73.0)	75.7 (167.0)	71.9 (158.5)
186.7 (73.5)	76.6 (169.0)	72.6 (160.2)
188.0 (74.0)	77.5 (171.0)	73.4 (161.8)
189.2 (74.5)	78.4 (172.8)	74.1 (163.4)
190.5 (75.0)	79.1 (174.5)	74.9 (165.1)
191.8 (75.5)	80.2 (176.8)	75.6 (166.8)
193.0 (76.0)	81.2 (179.0)	76.4 (168.4)
194.3 (76.5)	82.0 (180.8)	77.2 (170.1)
195.6 (77.0)	82.9 (182.9)	77.9 (171.8)
196.9 (77.5)	83.9 (185.0)	78.7 (173.5)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Adjusted Height* cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
198.1 (78.0)	84.9 (187.2)	79.5 (175.2)
199.4 (78.5)	85.9 (189.4)	80.3 (177.0)
200.7 (79.0)	86.9 (191.6)	81.0 (178.7)
201.9 (79.5)	87.9 (193.9)	81.8 (180.5)
203.2 (80.0)	89.0 (196.2)	82.6 (182.2)
204.5 (80.5)	90.0 (198.6)	*Height in shoes with one inch heels
205.7 (81.0)	91.1 (200.9)	*Indoor clothing weighing 5 pounds for men and 3 pounds for women
207.0 (81.5)	92.2 (203.3)	*Centimeters × 0.3937 = inches
208.3 (82.0)	93.3 (205.8)	*Pounds × 0.4535 = kilograms

Notes: * Values in the Adjusted Height column includes the 1" or 2.5 cm added to the height obtained during screening.

If the adjusted height falls in-between 2 values listed in the Adjusted Height column, the closest height listed on the chart should be selected.

Appendix E. Sample Injection Instructions for Onsite Administration – Pre-Filled Syringe

Subject Instructions

0.8 mL dose

(Administered as a single dose-pre-filled syringe)

Protocol M14-233

Tables of Contents

Injection Procedures (PFS)

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 prefilled syringe(s) of adalimumab from the refrigerator. Do not use a pre-filled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused syringe(s) to the refrigerator.

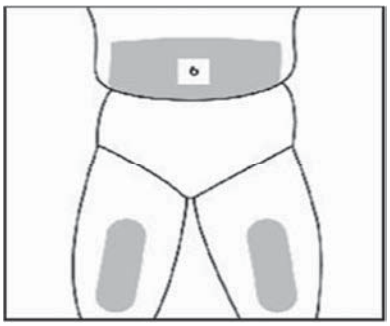
You will need the following items for each dose:

- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

- Use only the items provided in the box adalimumab comes in.
- Make sure the liquid in the pre-filled syringe is clear and colorless. Do not use a prefilled syringe 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 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 the thighs or stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches or 5 cm around your belly button (navel).
- Choose a different site each time you give an injection. Each new injection should be given at least one inch or 2.5 cm from a site used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If the subject has 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 the 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 Pre-filled Syringe

- Hold the syringe upright with the needle facing down. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study monitor.

- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- 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.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. There might be slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container.

Appendix F. Sample Injection Instructions for at Home Dosing – Pre-Filled Syringe

Subject Instructions

0.8 mL dose

(Administered as a single dose-pre-filled syringe)

Protocol M14-233

Tables of Contents:

Study Drug Dosing Schedule

Subject Number: _____

You will require subcutaneous injections throughout the study.

You will receive the following number of injections during the study:

- Baseline Visit (the first visit to receive study medication for this study), you will receive 4 injections (2 kits) at the clinic.
- Week 2 you will receive 2 injections (1 kit) at the clinic.
- At Week 4 you will receive 4 injections at the clinic.
- At Week 6 you will receive 2 injections at the clinic.
- At Week 8 you will receive 1 injection at the clinic.
- Week 10 you will administer 1 injection at home.
- At Weeks 12, 16, and 20 you will receive 1 injection at the clinic if you have not dose escalated. If you have dose escalated then you will receive 2 injections at the clinic.
- At Weeks 14, 18, 22, and 24 you will administer 1 injection at home if you have not dose escalated. If you have dose escalated then you will administer 2 injections at home.

For all doses, kits must be used in the order dispensed. All doses of study medication must be taken in order, starting with the syringe labeled with a "1," then at the next dose, using the syringe labeled with a "2."

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

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

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

General Information

- Pre-filled syringes will be labeled "Adalimumab" versus Placebo.
- Store all adalimumab pre-filled syringes in your refrigerator NOT in the freezer. Should the syringes 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 SYRINGE EVERY INJECTION DAY. There may be medication left in the syringe. DO NOT RE-USE.
- Save all study medications. ***Pre-filled syringes (used and unused) & 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.
- 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 (PFS)

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 prefilled syringe(s) of adalimumab from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused syringe(s) to the refrigerator.

You will need the following items for each dose:

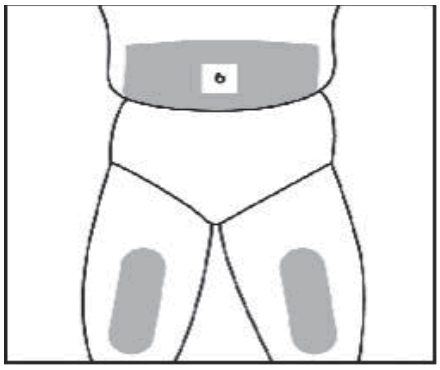
- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

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 prefilled syringe is clear and colorless. Do not use a prefilled syringe 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 or 5 cm around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch or 2.5 cm 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 Prefilled Syringe

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg prefilled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- 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.
- 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 special sharps container.

Appendix G. Sample Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ)

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME

7 NONE OF THE TIME

IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME

6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME

4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME

6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

Appendix H. 70-Day Follow-Up Phone Call – Sample

Site Name/Number: _____

Subject Number: _____

Please contact subjects that 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 one attempt.)
- ☐ No Events Reported.
- ☐ N/A subject continued adalimumab therapy after the end of their study participation.

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.

Please fax all completed forms to:

[Name] at XXX-XXX-XXXX

Appendix I. Protocol Amendment: List of Changes

Specific Protocol Changes

The summary of changes is listed in Section 1.1.

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

Has been changed to read:

Section 1.1 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Inclusion:"
Criterion 4, third bullet previously read:

At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of azathioprine ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available tablet formulation) or MTX ≥ 15 mg (subcutaneous [SC]/intramuscular [IM]) per week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Has been changed to read:

At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of azathioprine ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or MTX ≥ 15 mg/week (subcutaneous [SC]/intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Section 1.1 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Inclusion:"
"Note:" following third bullet previously read:

Note: If a subject is on both an oral corticosteroid and an immunosuppressant BOTH of the drugs need to meet the above criteria.

Has been changed to read:

Note: If a subject is on both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria.

Section 1.1 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Exclusion:"
Criterion 12 previously read:

Subject with prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], efalizumab [Raptiva®], or rituximab [Rituxan®]).

Has been changed to read:

Subject with prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®] or rituximab [Rituxan®]).

Section 1.1 Synopsis
Subsection Diagnosis and Main Criteria for Inclusion/Exclusion:
Heading "Main Exclusion:"
Criterion 31 previously read:

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

Has been changed to read:

Subject with a previous history of gastric dysplasia.

Section 3.3 Adalimumab Overview
Last paragraph, second sentence previously read:

Additional indications have been approved in the US and EU including Psoriasis (Ps), Psoriatic Arthritis (PsA), Ankylosing Spondyloarthritis (AS), CD, pediatric Crohn's Disease, polyarticular Juvenile Idiopathic Arthritis (JIA), and Ulcerative Colitis (UC).

Has been changed to read:

Additional indications have been approved in the US and EU including Psoriasis (Ps), Psoriatic Arthritis (PsA), Ankylosing Spondyloarthritis (AS), CD, Ulcerative Colitis (UC), polyarticular Juvenile Idiopathic Arthritis (JIA), pediatric CD, pediatric psoriasis as well as pediatric Enthesitis Related Arthritis and non-radiographic axial spondyloarthritis in the EU, and intestinal Bechet's Disease in Japan.

Section 5.1 Overall Study Design and Plan: Description
Subsection Re-screening
Fifth sentence previously read:

If the subject had a complete initial screening evaluation including the assessment of a QuantiFERON-Gold, CXR (or optional chest CT scan), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met.

Has been changed to read:

If the subject had a complete initial screening evaluation including the assessment of a QuantiFERON-TB Gold In-Tube test, CXR (or optional chest CT scan), and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met. If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 90 days of the re-screening visit. . If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors.

Section 5.2.1 Inclusion Criteria
Criterion 4, third bullet previously read:

At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of azathioprine ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available

tablet formulation) or MTX ≥ 15 mg (subcutaneous [SC]/intramuscular [IM]) per week, or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Has been changed to read:

At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of azathioprine ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or MTX ≥ 15 mg/week (subcutaneous [SC]/intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

Section 5.2.1 Inclusion Criteria
Criterion 4
"Note:" following third bullet previously read:

Note: If a subject is on both an oral corticosteroid and an immunosuppressant BOTH of the drugs need to meet the above criteria.

Has been changed to read:

Note: If a subject is on both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria.

Section 5.2.2 Exclusion Criteria
Criterion 12 previously read:

Subject with prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], efalizumab [Raptiva®], or rituximab [Rituxan®]).

Has been changed to read:

Subject with prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®] or rituximab [Rituxan®]).

Section 5.2.2 Exclusion Criteria
Criterion 31 previously read:

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

Has been changed to read:

Subject with a previous history of gastric dysplasia.

Section 5.2.3.3 Prohibited Therapy
Delete: eighth sub-bullet following first bullet

Efalizumab (Raptiva®);

Table 1. Study Activities
Activity "Pregnancy Tests[m]" previously read:

Activity	Screening (35 Days)	Day –21[a]	Day –7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Pregnancy Tests[m]	X[m]			X													X	X	

Has been changed to read:

Activity	Screening (35 Days)	Day –21[a]	Day –7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Pregnancy Tests[m]	X			X													X	X	

Table 1. Study Activities
Table note "n.," ninth and tenth sentence previously read:

Re-screen subjects with a negative anti-HIV-1 test results from the central lab within 90 days of initial Screening are not required to repeat HIV testing. Subjects with a negative anti-HIV-1 test results from the central lab within 90 days of Screening are not required to repeat HIV testing.

Has been changed to read:

If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors. If the subject had negative HBV and Anti-Hepatitis C test results from the central lab, these tests will not be required to be repeated if the results were obtained within 35 days of the re-screening visit.

Section 5.3.1.1 Study Procedures
Subsection TB Testing
First bullet previously read:

QuantiFERON-TB Gold In-Tube (QTF),

Has been changed to read:

QuantiFERON-TB Gold In-Tube test (QTF),

Section 5.3.1.1 Study Procedures
Subsection Crohn's Disease Activity Index (CDAI)
Seventh paragraph previously read:

Standard height is calculated by using the height obtained at Screening (without shoes) plus one inch.

Has been changed to read:

Standard height is calculated by using the height obtained at Screening (without shoes) plus one inch or 2.5 cm.

Section 5.3.1.1 Study Procedures
Subsection Hepatitis and HIV Testing
Third paragraph, last sentence previously read:

Subjects with negative anti-HIV-1 test results from the central lab within 90 days of Screening are not required to repeat HIV testing.

Has been changed to read:

If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors.

If the subject had negative HBV and Anti-Hepatitis C test results from the central lab, these tests will not be required to be repeated if the results were obtained within 35 days of the re-screening visit.

Section 5.3.1.1 Study Procedures
Subsection Other Laboratory Assessments
Heading "ANA/anti-dsDNA"
First paragraph, last sentence previously read:

Anti-double-stranded DNA (anti-dsDNA) assessments will be performed if ANA is positive (> 1/80).

Has been changed to read:

Anti-double-stranded DNA (anti-dsDNA) assessments will be performed if ANA is positive.

Section 5.3.1.2 Blood Samples for Pharmacogenetic Analysis
Second paragraph, second, third and fourth sentence previously read:

Samples will be shipped frozen to the central laboratory in China and then to AbbVie in China for long-term storage. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. Arrangements will be made with the central laboratory for the shipment of PG samples to AbbVie or specified lab for testing in China.

Has been changed to read:

Samples will be shipped frozen to the central laboratory in China and then to an AbbVie designated laboratory in China for long-term storage. Samples should not be allowed to thaw prior to arrival at the designated laboratory. Arrangements will be made with the central laboratory for the shipment of PG samples to the specified lab for testing in China.

Section 5.3.1.3 Blood Samples for Biomarkers Analysis
Subsection Collection of Samples for mRNA Analysis
Second paragraph, second, third and fourth sentence previously read:

Samples will be shipped frozen to the central laboratory in China and then to AbbVie in China for long-term storage. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. Arrangements will be made with the central laboratory for the shipment of PG samples to AbbVie or specified lab for testing in China.

Has been changed to read:

Samples will be shipped frozen to the central laboratory in China and then to an AbbVie designated laboratory in China for long-term storage. Samples should not be allowed to thaw prior to arrival at the designated laboratory. Arrangements will be made with the central laboratory for the shipment of mRNA samples to the specified lab for testing in China.

Section 5.3.5 Pharmacokinetic Variables
Add: new section

5.3.5 Pharmacokinetic Variables

Serum adalimumab concentrations will be determined from samples collected just prior to dosing at Baseline (Week 0), Week 4, Week 8, Week 12, and Week 26/Premature Discontinuation. Blood samples for the measurement of serum adalimumab concentrations at Week 14, Week 16, Week 18, Week 20, Week 22 and Week 24 will be collected prior to dosing only if the subject qualifies for dose escalation.

Serum anti-adalimumab antibody (AAA) will be determined from the samples collected just prior to dosing at Baseline (Week 0), Week 4, Week 12 and Week 26/Premature Discontinuation. Blood samples for the measurement of serum AAA at Week 14, Week 16, Week 18, Week 20, Week 22 and Week 24 will be collected prior to dosing only if the subject qualifies for dose escalation.

Blood samples will also be collected for measurement of infliximab serum levels and HACA just prior to dosing at Baseline (Week 0).

Section 5.4.1 Discontinuation of Individual Subjects
Ninth bullet, first sentence previously read:

Subject has dysplasia of the gastrointestinal tractor a malignancy, except for localized non-melanoma skin cancer.

Has been changed to read:

Subject has dysplasia or a malignancy, except for localized non-melanoma skin cancer.

Section 5.4.1 Discontinuation of Individual Subjects
Add: new second sentence to fourth paragraph

The information will be recorded on the appropriate eCRF page.

Section 6.1.5 Adverse Event Reporting
First paragraph, last sentence previously read:

Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger that occur prior to the site having access to the RAVE® system or if RAVE is not operable should use the SAE Non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Has been changed to read:

Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Section 6.1.5 Adverse Event Reporting
Contact information following first paragraph previously read:

[redacted]

Or

[redacted]

Or

FAX to: [redacted]

Section 6.1.5 Adverse Event Reporting
Fourth paragraph previously read:

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

[redacted]

Has been changed to read:

[redacted]

Section 7.0 Protocol Deviations
First paragraph, first sentence previously read:

AbbVie does not allow intentional/prospective deviations from the protocol.

Has been changed to read:

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects.

Appendix B. List of Protocol Signatories
Previously read:

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

Functional Area
Clinical
Statistics
Pharmacokinetics/Pharmacodynamics
Clinical
Clinical
Clinical

Appendix D. Standard Weights
Header row previously read:

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Actual Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**

Has been changed to read:

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Adjusted Height* cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**

Appendix D. Standard Weights
Table notes previously read:

Notes: Height in the Standard Height and Weight Tables includes the 1" or 2.5 cm added to the height obtained during screening.

If the actual measured height falls in-between 2 values listed under in the actual height column, the closest height listed on the chart should be selected.

Has been changed to read:

Notes: * Values in the Adjusted Height column includes the 1" or 2.5 cm added to the height obtained during screening.

If the adjusted height falls in-between 2 values listed in the Adjusted Height column, the closest height listed on the chart should be selected.

Appendix E. Sample Injection Instructions for Onsite Administration – Pre Filled Syringe
Subsection <u>Injection Procedures (PFS)</u>
Item 2, second and third bullet previously read:

- Choose a site on the front of the thighs or 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 an injection. Each new injection should be given at least one inch from a site used before. Never inject into

areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.

Has been changed to read:

- Choose a site on the front of the thighs or stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches or 5 cm around your belly button (navel).
- Choose a different site each time you give an injection. Each new injection should be given at least one inch or 2.5 cm from a site used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.

Appendix F. Sample Injection Instructions for at Home Dosing – Pre-Filled Syringe
Subsection <u>Injection Procedures (PFS)</u>
Item 2, second and third bullet previously read:

- 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 one 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.

Has been changed to read:

- 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 or 5 cm around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch or 2.5 cm 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.

Document Approval

Study M14233 - A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adalimumab for the Induction and Maintenance of Clinical Remission in Chinese Patients with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-reactive Protein - Amendment 1 - 19Oct2015

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Signed by:	Date:	Meaning Of Signature:
[redacted]	19-Oct-2015 07:25:02 PM	Approver
	19-Oct-2015 07:29:46 PM	Author
	19-Oct-2015 08:05:33 PM	Approver
	19-Oct-2015 09:25:43 PM	Approver
	19-Oct-2015 09:56:57 PM	Approver
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