1.0 Title Page

Clinical Study Protocol M14-115

A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration

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

AbbVie Investigational Product:	Adalimumab
Date:	27 November 2018
Development Phase:	3
Study Design:	A randomized, double-blind multicenter study of two adalimumab induction and maintenance dosing regimens in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration
EudraCT Number:	2013-001746-33
Investigators:	Multicenter. Investigator information is on file at AbbVie.

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

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	25 October 2013
Administrative Change 1	07 March 2014
Administrative Change 2	11 March 2014
Administrative Change 3	18 March 2014
Amendment 1	21 May 2014
Administrative Change 4	04 December 2014
Amendment 2	21 May 2015
Amendment 3	14 December 2015
Amendment 4	28 March 2016
Amendment 5	20 March 2017

The purpose of this amendment is to:

- Section 1.2, Synopsis: Clarify that all endpoints for the Exploratory Maintenance Study are non-ranked and correct error.

  Rationale: *To be consistent with existing methodology section within synopsis and Sections 5.3.3.2 and 5.3.3.3*
- Section 1.2, Synopsis, Section 4.0, Study Objective, Section 5.1, Overall Study Design and Plan: Description, Section 8.2, Determination of Sample Size: Update study sample size to 500, related power calculations and sample language.

  Rationale: *Sample size was updated based on adequacy of power assumed for updated endoscopic co-primary variable.*
- Section 1.2, Synopsis, Section 4.0, Study Objective, Section 5.3.3.1, Co-Primary Variables for Induction Study: Replace endoscopic co-primary variable.

  Rationale: *Update change in primary endoscopic endpoint.*

- Section 1.2, Synopsis, Section 5.3.3.2, Secondary Variables for Induction Study, ranked, Section 5.3.3.3, Endpoints for Exploratory Maintenance Study: Modify endoscopic portion of ranked secondary endpoint #2 and add an Exploratory Maintenance Study endpoint relating to endoscopic response.

  Rationale: *Update secondary and exploratory maintenance endpoints to reflect change in primary endoscopic endpoint.*

- Section 1.2, Synopsis, Section 5.3.3.2 Secondary Variables for Induction Study, ranked, Section 5.3.3.3, Endpoints for Exploratory Maintenance Study: Replace ranked secondary endpoint #5, and modify Exploratory Maintenance Study endpoint from endoscopic improvement to endoscopic remission.

  Rationale: *Update secondary and exploratory maintenance endpoints to reflect change in primary endoscopic endpoint.*

- Section 1.2 Synopsis, Section 4.0 Study Objective, Section 5.1 Overall Study Design and Plan: Description, Section 5.3.3.1, Co-Primary Variables for Induction Study, Section 5.3.3.2 Secondary Variables for Induction Study, Section 5.3.3.3 Endpoints for Exploratory Maintenance Study, Section 5.5.1 Treatments Administered, Section 8.1.4.1 Primary Efficacy Variable for Induction Study, Section 8.2 Determination of Sample Size, Section 8.3 Randomization Methods: Change instances of term endoscopic improvement, response, and remission throughout protocol and synopsis to reflect relevant endpoints.

  Rationale: *Align with study changes.*

- Section 1.2, Synopsis, Section 5.3.3.2 Secondary Variables for Induction Study, ranked: Modify ranked secondary endpoints #13 & #14 related to IBDQ.

  Rationale: *To focus on evaluation of bowel symptom domain of IBDQ that is directly related to the disease and relevant to IBD patients.*

- Section 1.2, Synopsis, Section 5.3.3.2 Secondary Variables for Induction Study, ranked: Add ranked secondary endpoint #15, proportion of subjects achieving response in IBDQ fatigue item at Week 12.

  Rationale: *To include fatigue in the evaluation as it is considered relevant to IBD patients and may provide information complimentary to the primary endpoint.*

- Section 1.2, Synopsis, Section 5.3.3.2 Secondary Variables for Induction Study, non-ranked, Section 5.3.3.3 Endpoints for Exploratory Maintenance Study: Add and modify non-ranked secondary endpoints related to IBDQ in Induction and Exploratory Maintenance, and delete a duplicate endpoint in Exploratory Maintenance.

  Rationale: *To examine the effect of treatment on various aspects of patients' life as measured by IBDQ total score and domain scores, as well as the fatigue item in IBDQ.*

- Section 5.3.3.2 Secondary Variables for Induction Study, non-ranked, Section 5.3.3.3 Endpoints for Exploratory Maintenance Study: Clarify name of score in non-ranked additional efficacy endpoints from "Bristol Stool Scale" to "Bristol Stool Chart score."

  Rationale: *To provide better clarity and consistency with the SAP.*

- Section 5.3.3.2 Secondary Variables for Induction Study, non-ranked: Add non-ranked efficacy endpoint regarding Bristol Stool Chart Score.

  Rationale: *Add second method to measure subjects who have response in stool consistency.*

- Section 5.3.3.2 Secondary Variables for Induction Study, non-ranked, Section 5.3.3.3 Endpoints for Exploratory Maintenance Study: Modify non-ranked additional efficacy endpoint definition of symptomatic remission and specify the Baseline stool frequency and abdominal pain score for symptomatic remission and response analyses at each scheduled visit in Induction and Maintenance Study respectively.

  Rationale: *Modify non-ranked efficacy endpoint definition for symptomatic remission and response to align with current AbbVie IBD registrational trials.*

- Section 5.3.3.3 Endpoints for Exploratory Maintenance Study: Add additional non-ranked efficacy endpoints at Week 56 related to subjects requiring dose escalation to weekly dosing during Maintenance Study.

  Rationale: *To assess the effect of dose escalation.*

- Section 5.2.3.2, Concomitant Therapy: Update Prior and Concomitant Therapy section to specify details regarding concomitant medications and censoring.

Rationale: *Align censoring rules according to current AbbVie conventions.*

- Section 5.3.1 Table 3. Corrected error in Study Activities Table, for activity Study Drug Dispensing/Administration"s"

  Rationale: *Clarify that the "s" in Study Drug Dispensing/Administration"s" should be a superscript "s" and correspond to footnote "s."*

- Section 5.5.2.2, Storage and Disposition of Study Drug: Clarify that only temperature excursions greater than 30 minutes need to be reported to the sponsor.

  Rationale: *Align with new AbbVie guidance developed following a cross-functional risk evaluation.*

- Section 7.0, Protocol Deviations: Update alternate contact.

  Rationale: *Update to include current study contact information.*

- Section 8.1.7, Interim Analysis: Information added to describe Interim Analysis which may be performed via a database cut

  Rationale: *To reflect a possibility to perform an interim analysis for the induction study and clarify the process.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-115
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 27 November 2018
Protocol Title: A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration	
Objectives: The objective of Study M14-115 is to evaluate efficacy and safety of higher induction and maintenance dosing regimens in subjects with moderately to severely active Crohn's disease.	
Investigators: Multicenter	
Study Sites: Approximately 150 sites worldwide.	
Study Population: Males and females ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active Crohn's disease, CDAI ≥ 220 and ≤ 450, and evidence of mucosal ulceration by Simple Endoscopic Score (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on screening endoscopy (or endoscopy performed within 45 days before Baseline), confirmed by a central reader.	
Number of Subjects to be Enrolled: Approximately 500 (300 in higher induction regimen group and 200 in standard induction regimen group) subjects with moderately to severely active Crohn's Disease, CDAI of ≥ 220 and ≤ 450 and evidence of mucosal ulceration, confirmed by centrally read endoscopy.	
Methodology: This Phase 3 study design includes the Screening Period followed by a 12-Week double-blind Induction Study and 44-Week double-blind Maintenance Study. The Induction Study will assess the efficacy and safety of two adalimumab induction regimens in achieving clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150 at Week 4, and endoscopic response, defined as a decrease in Simplified Endoscopic Score for Crohn's Disease (SES-CD) > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer, at Week 12; in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration at Baseline. The Maintenance Study will assess the efficacy and safety of two adalimumab maintenance regimens in maintaining clinical and endoscopic improvements at Week 56. Analyses of the outcomes from the maintenance regimens are considered exploratory. During both the Induction Study and the Maintenance Study, visit week designations will represent weeks since first dose in the Induction Study. Week 0 (Baseline) will reflect the date of first adalimumab dosing in the Induction Study. Week 12 will represent the final assessment in the Induction Study. Week 56 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study).	

Methodology (Continued):

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 3:2 ratio at Baseline to receive a higher induction adalimumab regimen or standard induction adalimumab regimen during the double-blind Induction Study. Up to 25% of subjects with previous infliximab exposure may be enrolled. All subjects who complete the Induction Study (regardless of achievement of response at Week 12) will continue into the Maintenance Study. Assuming the Week 4 clinical remission rate will be approximately 50% for the higher induction dose regimen and approximately 30% for the standard dose regimen, a sample size of 500 (300 higher dose and 200 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts an expected ~50% increase in the proportion of subjects with endoscopic response compared to the standard adalimumab induction regimen. The observed rate of endoscopic response in Study M05-769 was 44% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for endoscopic response at Week 12 using the higher induction regimen is 66%. A sample size of 500 subjects (300 higher induction regimen and 200 standard induction regimen) will be adequate to detect at least a 22% treatment difference in endoscopic response rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 99% power at a 0.05 two-sided significance level.

Since clinical remission at the Week 4 endpoint and the endoscopic response at the Week 12 endpoint are not likely to be independent of each other, the power for the co-primary endpoints for the Induction Study is expected to be > 98% (see protocol for detailed assumptions of the sample size calculation).

The randomization of subjects for the Induction Study will be stratified by high-sensitivity C-Reactive Protein (hs-CRP) at Baseline (< 10 and ≥ 10 mg/L), using the Screening hs-CRP value, prior infliximab use, and Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline. Subjects with prior infliximab experience will be limited to 25% of the study population. Subjects assigned to the higher induction regimen will receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects will receive adalimumab 40 mg every other week (eow) through Week 12. Subjects assigned to the standard induction regimen will receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg at Week 2 and matching placebo at Week 3. At Week 4, subjects will receive adalimumab 40 mg every other week through Week 12.

<u>Maintenance Study:</u>

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of the two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen). The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Methodology (Continued):

Clinically Adjusted (CA) Regimen:

Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week (ew) as early as Week 14 if the subject's CDAI ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria below. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing.

Therapeutic Drug Monitoring (TDM) Regimen:

At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM will be determined by the dose adjustment criteria referenced in the table below. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.

The goal of the TDM regimen is to attain and maintain serum adalimumab levels above a reasonably high concentration levels in subjects for mucosal healing. Since exposure-endoscopic relationships are not currently available for adalimumab, clinical remission was used for selection of concentration threshold to be used in TDM arm. Based on the PK analyses of concentrations in Studies M02-403, M04-691 and M02-433, no concentration level could be identified as significant and reliable predictor of remission in adult CD. Therefore, the TDM regimen will be based on two concentration thresholds in conjunction with clinical response criteria as expected to occur in clinical setting. About 75% of the subjects who were in remission at Week 56 in Study M02-433 had serum concentration above 5 µg/mL. Therefore, the lower concentration threshold for the TDM regimen was selected as 5 µg/mL and any subject below 5 µg/mL concentration will be escalated to ew dosing. The second threshold was selected as 10 µg/mL, which is similar to the median concentrations (9.4 µg/mL at Week 56) observed in subjects who were in remission. The subjects with concentration above 5 and below 10 µg/mL may be dose escalated based on clinical response as outlined in the table below. The subjects with serum concentration above 10 µg/mL will not be dose escalated.

Methodology (Continued):

Adalimumab Dose Adjustment Criteria[a]

ADA Serum Concentration[b] (ug/mL)	CDAI[c]	hs-CRP[d] (mg/L)	Dose Change?
Clinically Adjusted Regimen			
any	< 220	< 10	no
any	any	≥ 10	yes; dose escalate to ew
any	≥ 220	any	yes; dose escalate to ew
Therapeutic Drug Monitoring Regimen			
< 5	any	any	yes; dose escalate to ew
5 – 10	< 220	< 10	no
5 – 10	any	≥ 10	yes; dose escalate to ew
5 – 10	≥ 220	any	yes; dose escalate to ew
> 10	any	any	no

a. For subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable, the investigator should contact the Study Designated Physician.

b. Measured from the serum concentration taken at the prior study visit.

c. Measured using hematocrit taken from prior study visit for CDAI calculation.

d. Measured using hs-CRP from the prior or current study visit.

The duration of the study could be up to 60 weeks which includes a Screening Period (1 – 4 weeks), a 12-week double-blind Induction Study and a 44-week Maintenance Study. The Screening Period may be extended as necessary after consultation with and approval by the AbbVie Study Designated Physician (SDP) for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results). There will also be a 70-day follow-up phone call for subjects who complete Week 56 or discontinue from the study prematurely.

Clinical evaluation will occur at Baseline, Weeks 2, 4, 6, 8, 12, 14, 20, 26, 28, 34, 40, 42, 48, and 56/Premature Discontinuation (PD) visits. An electronic diary will be dispensed at the Screening visit. In addition to routine physical examination, CDAI calculation, diary review, laboratory, adverse event, concomitant medication and vital sign assessments, the following will be collected:

- Results of study questionnaires (IBDQ, EQ-5D, WPAI) at Baseline, Week 4, Week 8, Week 12, Week 26, Week 40 and Week 56/PD.
- Calculation of the SFPS at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 14, Week 20, Week 26, Week 28, Week 34, Week 40, Week 42, Week 48 and Week 56/PD. The Screening visit results will serve as the Baseline value.
- Results of daily Bristol Stool Form Scale beginning at Baseline through Week 56/PD.
- Results of 11-point Abdominal Pain Rating Scale beginning at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.

Methodology (Continued):

- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.
- Serum biomarkers/mRNA at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Stool samples for analysis of fecal calprotectin during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Stool samples for microbiota metagenomic analyses during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Endoscopic evaluations, confirmed by central reader, will be done at Screening, Week 12, and Week 56/PD.
- An optional pharmacogenetic sample should be drawn at Baseline and Week 12.

Throughout the study, subjects will only be allowed to change the dosage of CD-specific concomitant medications as specified below:

- At Week 4, subjects who are taking corticosteroid therapy at Baseline will have their corticosteroid therapy tapered according to a tapering schedule specified in the clinical study protocol. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the Study Designated Physician (SDP) should be consulted for evaluation and approval.
- Subjects taking corticosteroids at Baseline who have a loss of satisfactory clinical response per the Investigator's judgment after the steroid taper has been initiated may have their corticosteroid dose increased per the Investigator's discretion during the study. Subjects in whom the maximum equivalent steroid dose exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion

1. Males and females ≥ 18 and ≤ 75 years of age at Baseline.
2. Diagnosis of colonic, ileocolonic, or ileal Crohn's disease for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before Baseline, with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Simplified Endoscopic Score for Crohn's Disease (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on a screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader.

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

Main Inclusion (Continued)

4. Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450 at Baseline despite concurrent or prior treatment with a full and adequate course, in the opinion of the Investigator, of at least one of the following (oral corticosteroids and/or immunosuppressants or both as defined below):
   - Subject taking oral corticosteroids, excluding budesonide:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subjects with a dose > 10 and ≤ 40 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 and the duration of the current steroid course has been at least 14 days prior to Baseline.
   - Subject 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 and the duration of the current steroid course has been at least 14 days prior to Baseline;

   or,

   - At least a consecutive 42-day course of azathioprine, 6-MP or injectable MTX prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of at least 230 pmol/8 × 10^8 RBC to clarify a therapeutic level was achieved on the current dosing regimen 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.

     Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.

   or,

   - Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability, see Section 10.1.

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

Main Inclusion (Continued):

5. Subject may be included if they have previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD-related symptoms) or intolerance (in the opinion of the Investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. Subject has a negative TB Screening Assessment (including a PPD test or QuantiFERON TB Gold test [or equivalent]) and negative chest x-ray (CXR – PA and lateral view) at Screening. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.
7. 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 which result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
   - Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone releasing system (IUS)
   - Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
   - Vasectomized partner
   - Hormonal contraceptives for at least 90 days prior to study drug administration.

   Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol 0.5 mg are not considered adequate.
8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
9. Subject is judged to be in otherwise good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead electrocardiogram (ECG) performed during Screening.
10. 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 on azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who:
   - Has not been on these medications for at least 42 days prior to Baseline; or
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued these medications within 14 days of Baseline.

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

Main Exclusion (Continued):

3. Subject on oral aminosalicylates who:
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued use of aminosalicylates within 14 days of Baseline.
4. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide > 9 mg/day; or
   - Subject taking an oral corticosteroid (excluding budesonide):
     - dose > 10 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose > 10 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent, but has **not** been on a stable dose for at least 10 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline, or
   - Subject taking budesonide:
     - dose ≥ 6 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose ≥ 6 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose < 6 mg/day dose but has **not** been on a stable dose of at least 10 days prior to Baseline; or
     - dose < 6 mg/day but the current course has **not** been at least 14 days in duration prior to Baseline; or

   Has been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of inhalers.
5. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
6. Subject who has had surgical bowel resections within the past 6 months or is planning any resection at any time point while enrolled in the study.
7. Subject with a symptomatic bowel stricture.
8. Subject with an abdominal or peri-anal abscess.
9. Subject with an ostomy or ileoanal pouch.
10. Subject who has 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 (PML) including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab [Raptiva®]). Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).

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

Main Exclusion (Continued):

13. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.
14. Subject who previously received treatment with adalimumab or previously participated in an adalimumab clinical study.
15. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 60 days prior to Baseline.
16. Subject who previously received stem cell transplantation.
17. Subject who previously received fecal microbial transplantation.
18. Subject that received non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days prior to Screening and during the Screening Visit, except low-dose aspirin for prevention of heart attacks, unstable angina or transient ischemic attacks or topical NSAIDs.
19. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives for non-Crohn's disease related infections within 14 days prior to the Baseline Visit.
20. Subjects on Crohn's disease related antibiotics that have not been on stable doses for at least 28 days prior to Baseline. Subjects on Crohn's disease related antibiotics that have discontinued these medications within 28 days of Baseline are excluded.
21. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.
22. Subject with positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening period.
23. Screening laboratory and other analyses show any of the following abnormal results:
    - AST, ALT > 1.75 × 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.
24. Known hypersensitivity to adalimumab or its excipients.
25. Subject who has previously used infliximab:
    - and had not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction;

      or
    - who used infliximab within 56 days of Baseline.
26. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
27. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).
28. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

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

Main Exclusion (Continued):

29. Subjects with a positive result for the Hepatitis B surface antigen (HBs Ag) will be excluded. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

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

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

        * For HBs Ab test results, a (–) result is equivalent to nonreactive and a (+) result is equivalent to reactive.

30. Chronic recurring infections.
31. Subject with active TB.
32. Subject with latent TB infection unless there is evidence the subject initiated and completed a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.
33. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study.
34. Subject with a previous history of dysplasia of the gastrointestinal tract, or found to have dysplasia in any biopsy performed during the Screening endoscopy or endoscopy performed within 45 days before Baseline.
35. Positive pregnancy test at Screening (serum) or Baseline (urine).
36. Female subjects who are breastfeeding or considering becoming pregnant during the study.
37. History of clinically significant drug or alcohol abuse in the last 12 months.
38. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
39. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
40. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Products:	Adalimumab (40 mg/0.8 mL)
Double-Blind Induction	Subjects will be randomized to receive one of 2 double-blind adalimumab Induction Study regimens.
Doses:	**(Higher Induction Regimen)** 160 mg at Baseline, Weeks 1, 2, and 3, and 40 mg at Week 4, continuing at 40 mg every other week through Week 12. **(Standard Induction Regimen)** 160 mg at Baseline and matching placebo at Week 1, 80 mg at Week 2 and matching placebo at Week 3 and 40 mg every other week beginning at Week 4 through Week 12.
Double-Blind Maintenance	Subjects will receive one of two double-blind adalimumab Maintenance Study regimens.
Doses: NOTE: In order to retain blinding across regimens, all subjects who do not meet the criteria for dose escalation in either maintenance regimen will receive matching placebo injections in addition to the adalimumab injection.	Clinically Adjusted (CA) Regimen: Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week starting at Week 14 if CDAI is ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria table. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing. Therapeutic Drug Monitoring (TDM) Regimen: At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM regimen will be determined by the dose adjustment criteria table. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment:

The study will include a Screening Period of 1 – 4 weeks, a double-blind Induction Study of 12 weeks, and a double-blind Maintenance Study of 44 weeks. There will also be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely.

Criteria for Evaluation:

Efficacy Endpoints:

Subjects participating in the Induction Study randomized to the higher adalimumab induction dose regimen will be compared to those subjects randomized to the standard adalimumab induction regimen. Subject data from the Maintenance Study will be used for exploratory analyses.

Induction Study Co-Primary Efficacy Endpoints:

- Proportion of subjects who achieve a CDAI < 150 at Week 4.
- Proportion of subjects with decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.

Induction Study Ranked Secondary Endpoints:

1. Proportion of subjects with sustained clinical remission (CDAI < 150) at both Weeks 4 and 12.
2. Proportion of subjects with CDAI < 150 at Week 4 and decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.
3. Proportion of subjects with clinical remission (CDAI < 150) at Week 12.
4. Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 12 among subjects taking corticosteroids at Baseline.
5. Proportion of subjects with endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 12.
6. Change from Baseline in fecal calprotectin level at Week 4.
7. Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 μg/g at Week 4.
8. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g at Week 4.
9. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore > 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 12.
10. Proportion of subjects who achieve an SES-CD ≤ 2 at Week 12.
11. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 4.
12. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 12.
13. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 4.
14. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 12.
15. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 12.

All other efficacy and exploratory endpoints will be non-ranked.

Criteria for Evaluation (Continued):

All endpoints for the Exploratory Maintenance Study will be non-ranked.

Pharmacokinetic:

Blood samples will be collected for measurement of serum adalimumab concentration just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/Premature Discontinuation and anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56PD.

Blood samples will also be collected for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.

Exploratory Research Using Intestinal Mucosal Biopsy Samples (Optional):

Optional intestinal biopsies will be collected with consent at Screening, Week 12, and Week 56 or at premature discontinuation. The purpose of these samples is to test potential biomarker signatures and new drug targets for IBD. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

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 co-primary efficacy variables for the Induction Study are proportion of subjects with moderately to severely active CD that have achieved clinical remission, defined as CDAI < 150, at Week 4 and proportion of subjects with moderately to severely active CD that have achieved a decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), at Week 12. The comparison between treatment groups for the two co-primary efficacy variables will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by hs-CRP at Baseline (< 10 and ≥ 10 mg/L) (the Screening hs-CRP will serve as the Baseline value), prior infliximab use, and Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline. 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. For the evaluation of co-primary endpoints, missing data of CDAI at Week 4 or missing SES-CD at Week 12 will be imputed using the non-responder imputation (NRI) approach. For Week 4 clinical remission, LOCF, OC and multiple imputation methods will be used as sensitivity analyses. For Week 12 endoscopic response (decrease in SES-CD > 50% from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]), OC will be used as sensitivity analysis.

Statistical Methods (Continued):

Efficacy (Continued):

Secondary efficacy variables for the Induction Study are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at significance level of 0.050 (2-sided) in ranked endpoint order until the significance level exceeds 0.05. No additional statistically significant treatment differences may be declared after the first ranked endpoint fails to achieve statistical significance at a two-sided significance level of 0.05. The second group includes all other secondary variables.

In general, continuous secondary efficacy variables, including all efficacy variables for Maintenance Study, 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 is used for categorical endpoints. NRI for missing data will be used for categorical endpoints. Both last observation carried forward (LOCF) and observed case (OC) analyses will be performed for continuous endpoints. The LOCF analysis is considered primary for inferential purposes. In addition, Mixed-Effect Model Repeated Measure (MMRM) will be applied, wherever appropriate, as a sensitivity analysis for the longitudinal continuous endpoints.

Pharmacokinetic:

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

Immunogenicity:

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

Safety:

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

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 for subjects who do not participate in the OLE or until first dose of study drug in the OLE study if the subject is a study completer and is enrolled in the OLE. Treatment-emergent AEs will be summarized separately for: a) Baseline to Week 12; b) Week 12 to Week 56; c) Baseline to Week 56 (overall study duration). An overview of treatment-emergent AEs, including AEs of special interest, adverse events leading to death and adverse events leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 20.1 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.

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.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-mercaptopurine
6-TGN	6-thioguanine
AAA	Anti-adalimumab antibody
ADA	Adalimumab
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibody
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
BUN	Blood urea nitrogen
CA	Clinically Adjusted
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDC	Centers for Disease Control and Prevention
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-Reactive Protein
CXR	Chest x-ray
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIM	Extra-Intestinal Manifestations
eow	Every other week
ePRO	Electronic Patient Reported Outcome
EQ-5D	European Quality of Life 5 Dimensions
ew	Every Week
FDA	Food and Drug Administration

GCP	Good Clinical Practice
HACA	Human Anti-Chimeric Antibody
HBV	Hepatitis B virus
HBc Ab	Hepatitis B core antibodies
Hbs Ab	Hepatitis B surface antibodies
Hbs Ag	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
MTX	Methotrexate
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
OC	Observed Case
OLE	Open-Label Extension
PA	Posteroanterior
PD	Premature Discontinuation
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
POR	Proof of Receipt
PPD	Purified protein derivative
RA	Rheumatoid arthritis
RBC	Red blood cell

SAE	Serious adverse event
SC	Subcutaneous
SDP	Study designated physician
SES-CD	Simplified endoscopic score for Crohn's disease
SFPS	CDAI components "Number of liquid or very soft stools" and "Abdominal pain" (Stool [liquid/soft] Frequency + Abdominal Pain Score; SFPS)
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
UC	Ulcerative Colitis
WBC	White blood cell

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3.0 Introduction

Crohn's disease 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.[2,3] In North America, the incidence of CD is estimated to be 3.1 to 14.6 cases per 100,000 persons.[2] 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.[2]

Traditionally, therapy for CD has been focused on symptomatic improvement and achievement of clinical remission as measured using the CDAI. In addition to improving symptoms, an emerging goal of therapy is to improve the condition of the intestinal mucosa. It has been shown that patients with endoscopic evidence of ulceration of the gastrointestinal mucosa are at increased risk of experiencing a complicated disease course.[4] Therefore, it is reasonable that another goal of therapy be improvement of the intestinal mucosal as visualized on endoscopy; as this has been found to be associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries.[5,6] In addition, at the 2012 United States (US) Food and Drug Administration (FDA)-sponsored Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) Workshop, there was significant discussion on the use of endoscopy to support determination of disease activity, as opposed to using symptomatic improvements alone. However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone as it requires reducing the extent of mucosal ulceration. A new endpoint for efficacy of therapy was discussed at the Organization for the Study of Inflammatory Bowel Disease (IOIBD); the achievement of mucosal remission measured as SES-CD of ≤ 2.0.[9] This endpoint was added to the Induction Study and as an exploratory endpoint in the Maintenance study.

Comparison of various efficacy endpoints assessed in the EXTEND study (Study M05-769) suggests that when raising the efficacy standard from one that is driven by symptoms to one that is more objective (i.e., assessment of improvement in the condition of the intestinal mucosa), there is an overall decrease in both efficacy rate and effect size for adalimumab.[7]

Table 1. Efficacy Rates at Week 12 (ITT) of the M05-769 Study

	Placebo	ADA 160/80	Effect Size	*P* Value
Clinical Remission[a] n/N (%)	18/65 (28)	30/64 (47)	19	0.021
Mucosal Healing[b] n/N (%)	8/61 (13)	17/62 (27)	14	0.056

ITT = intent-to-treat

a. Defined as CDAI < 150.

b. Defined as absence of mucosal ulceration as confirmed by central reader's visual assessment of the ileocolonoscopy.

Note: Four patients randomized to placebo and 2 patients randomized to ADA were excluded from the mucosal healing analysis as they had absence of mucosal ulceration at screening (as judged by the review committee).

Exposure-response analyses based on adalimumab trough serum concentration and Crohn's disease activity index (CDAI)-based efficacy (remission, CR-70 and CR-100) at Week 4 conducted with data from previous adalimumab induction studies (CLASSIC [Study M02-403] and GAIN [Study M04-691]) have shown that higher Week 4 efficacy rates corresponded to higher adalimumab trough serum concentrations in both anti-TNF naïve and anti-TNF experienced subjects. Therefore, to improve the likelihood of achieving more stringent efficacy endpoints, such as endoscopic improvement of the intestinal mucosa, more intensive treatment with adalimumab may be required.

For the reasons described above, this study is designed to investigate the efficacy and safety of two adalimumab induction regimens (higher and standard) in adult subjects with moderately to severely active CD and evidence of mucosal ulceration. Additionally, the study will evaluate the sustained efficacy of the standard maintenance therapy of 40 mg adalimumab dosing every other week with subjects whose dosing is either guided by trough adalimumab concentrations (Therapeutic Drug Monitoring regimen) or by clinical assessment without adalimumab concentrations (Clinically Adjusted regimen).

3.1 Differences Statement

The primary difference between Study M14-115 and the other CD studies, are the inclusion of subjects with evidence of mucosal ulceration defined as SES-CD ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader. Subjects would be required to have presence of ulceration confirmed by central reader prior to Baseline. An additional difference is the inclusion of an induction regimen higher than has previously been studied in CD in the 12 week Induction Study. For the first time in a blinded study, the Maintenance Study of this protocol presents the option to adjust adalimumab dosing from eow to ew based on trough adalimumab concentrations as compared to adjustment based on clinical assessment of hs-CRP and CDAI.

3.2 Benefits and Risks

Extensive clinical and post marketing experience exists with adalimumab in a wide range of disease states including Crohn's disease 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 current 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 1,330 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).

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) and serum cytokines rapidly decrease.

Adalimumab was first approved in US and 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, psoriatic arthritis, axial spondylitis, Crohn's Disease, ulcerative colitis, polyarticular Juvenile Idiopathic Arthritis, pediatric Crohn's Disease, pediatric psoriasis as well as pediatric enthesitis related arthritis and non-radiographic axial spondyloarthritis in EU only and intestinal Beçhet'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 in adults based on extensive post marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. 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 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 Objective

The primary objective of this study is to assess the efficacy and safety of two adalimumab induction regimens in achieving clinical remission (CDAI < 150) at Week 4 and endoscopic response defined as decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12, in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration at Baseline.

Additional objectives include:

- Assessing the efficacy and safety of two adalimumab induction regimens in reducing signs and symptoms of Crohn's disease at Week 12.
- Assessing the efficacy and safety of two adalimumab maintenance regimens in reducing signs and symptoms of Crohn's disease at Week 56.
- Assessing pharmacokinetics (PK) and immunogenicity of two adalimumab induction regimens following subcutaneous (SC) administration.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a randomized, double-blind multicenter study of two adalimumab induction and maintenance regimens in subjects with moderately to severely active CD with evidence of mucosal ulceration confirmed by central reading. No placebo arm is planned since there is well-documented efficacy of adalimumab in CD and because the purpose of this study is to achieve better efficacy than the standard induction and maintenance regimens in

terms of clinical remission and endoscopic response. Additionally, since subjects will be required to have failed or been intolerant of standard therapies and have evidence of endoscopic damage confirmed by a central reader, it would be not medically acceptable to deny those subjects effective treatment or feasible to enroll subjects in the trial when adalimumab is available to be prescribed for CD.

Approximately 500 adult subjects with active Crohn's disease, defined as having a CDAI of ≥ 220 and ≤ 450 and evidence of mucosal ulceration defined as SES-CD ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a centrally read endoscopy, will be enrolled at approximately 150 sites worldwide.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 3:2 ratio at Baseline to receive a higher induction adalimumab regimen or standard induction adalimumab regimen during the double-blind Induction Study. Assuming the Week 4 clinical remission rate will be approximately 50% for the higher induction dose regimen and approximately 30% for the standard dose regimen, a sample size of 500 (300 higher dose and 200 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts an expected ~50% increase in the proportion of subjects with endoscopic response compared to the standard adalimumab induction regimen. The observed rate of endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) in Study M05-769 was 44% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for endoscopic response at Week 12 using the higher induction regimen is 66%. A sample size of 500 subjects (300 higher induction regimen and 200 standard induction regimen) will be adequate to

detect at least a 22% treatment difference in endoscopic response (decrease >50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 99% power at a 0.05 two-sided significance level.

Since the clinical remission at Week 4 endpoint and the endoscopic response at Week 12 endpoint are likely not independent of each other, the power for the co-primary endpoints for the study is expected to be > 98% (see Section 8.2 for detailed assumptions of the sample size calculation).

The randomization of subjects for the Induction Study will be stratified by hs-CRP at Baseline (< 10 and ≥ 10 mg/L), using the Screening hs-CRP value, prior infliximab use, and Crohn's disease activity (CDAI ≤ 300, > 300), at Baseline. Enrollment of subjects with prior infliximab use will be limited to 25% of the total study population.

Subjects assigned to the higher induction regimen will receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects will receive 40 mg every other week (eow) through Week 12. Subjects assigned to the standard adalimumab induction regimen will receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1. Subjects will receive 80 mg and matching placebo at Week 2, and then matching placebo at Week 3. At Week 4, subjects will receive 40 mg every other week through Week 12.

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of the two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen). The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus Baseline and no subscore greater than 1 in any

individual variable using the Week 12 SES-CD value provided by the site. No study drug will be administered or injected at the final visit.

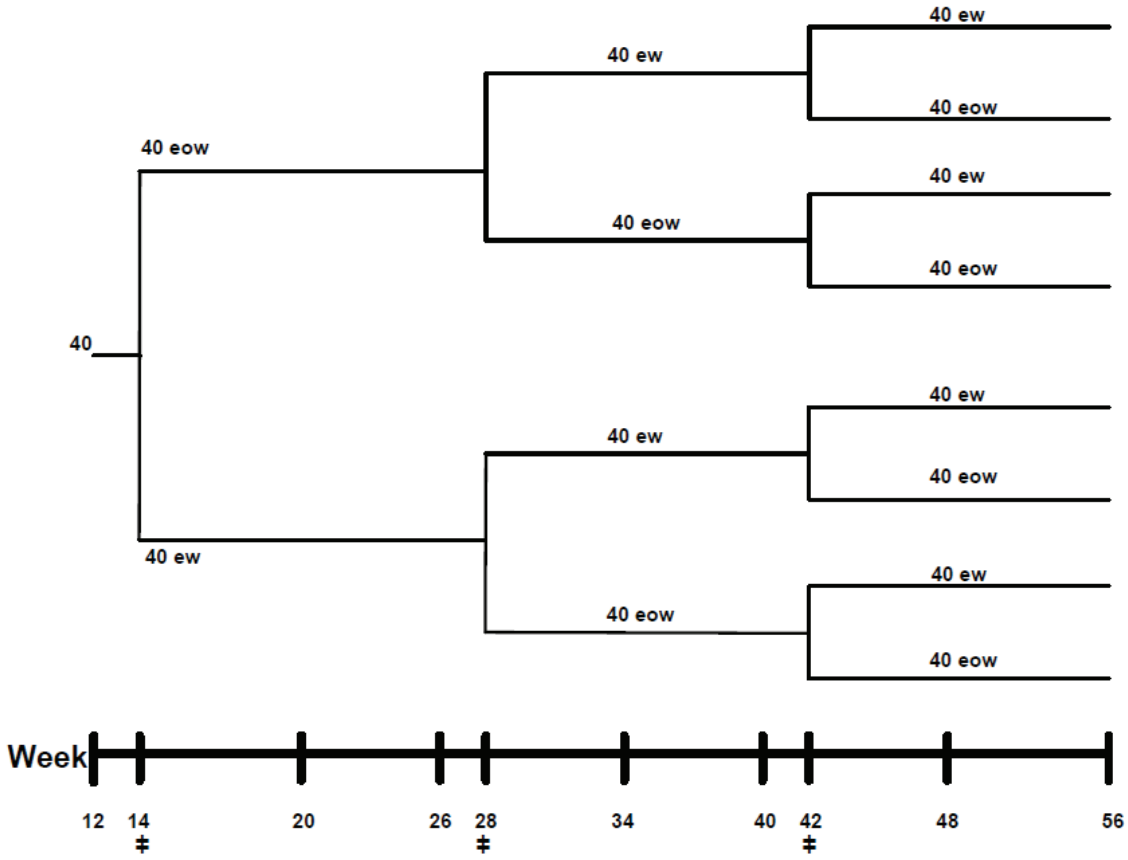
Clinically Adjusted (CA) Regimen:

Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week starting as early as Week 14 if the subject's CDAI is ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit). These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the CA regimen are escalated, they will remain on 40 mg ew dosing.

Therapeutic Drug Monitoring (TDM) Regimen:

At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM will be determined by the dose adjustment criteria table (Table 2). Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.

Figure 1. Therapeutic Drug Monitoring (TDM) Regimen Schematic



‡ Adjust dose based on labs taken 2 weeks prior

Table 2. Adalimumab Dose Adjustment Criteria

Adalimumab Dose Adjustment Criteria[a]			
ADA Serum Concentration[b] (ug/mL)	**CDAI[c]**	**hs-CRP[d] (mg/L)**	**Dose Change?**
Clinically Adjusted Regimen			
any	< 220	< 10	no
any	any	≥ 10	yes; dose escalate to ew
any	≥ 220	any	yes; dose escalate to ew
Therapeutic Drug Monitoring Regimen			
< 5	any	any	yes; dose escalate to ew
5 – 10	< 220	< 10	no
5 – 10	any	≥ 10	yes; dose escalate to ew
5 – 10	≥ 220	any	yes; dose escalate to ew
> 10	any	any	no

a. For subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable, the investigator should contact the Study Designated Physician.

b. Measured from the serum concentration taken at the prior study visit.

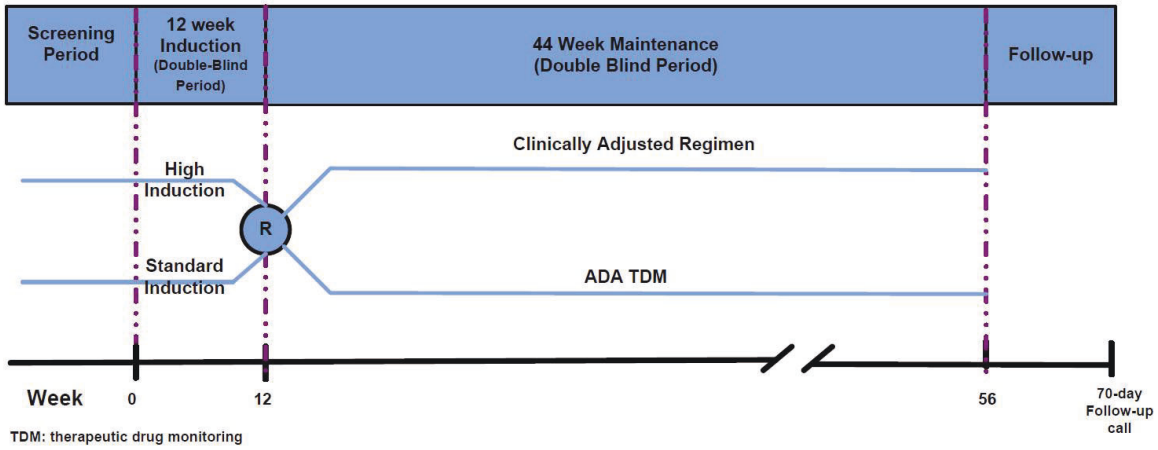
c. Measured using hematocrit taken from prior study visit for CDAI calculation.

d. Measure using hs-CRP from the prior or current study visit.

The duration of the study could be up to 60 weeks which includes a Screening Period (1 – 4 weeks, ± 3 days which is granted around all study visits), a 12 week double-blind period Induction Study, and a double-blind 44-week Maintenance Study. The Screening Period may be extended as necessary after consultation and approval with the AbbVie Study Designated Physician (SDP) for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results). There will also be a 70-day follow-up phone call for subjects who complete Week 56 or discontinue from the study prematurely.

A schematic of the study design is presented in Figure 2.

Figure 2. Study Schematic



Clinical evaluation will be at visits occurring at Baseline, Weeks 2, 4, 6, 8, 12, 14, 20, 26, 28, 34, 40, 42, 48, and 56/PD. An electronic diary will be dispensed at the Screening visit. In addition to routine physical examination, CDAI calculation, diary review, laboratory, adverse event, concomitant medication and vital sign assessments, the following will be collected:

- Results of study questionnaires (inflammatory bowel disease questionnaire [IBDQ], European Quality of Life 5 dimensions [EQ-5D], work productivity and impairment [WPAI]) at Baseline, Week 4, Week 8, Week 12, Week 26, Week 40 and Week 56/PD.
- Calculation of the SFPS at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 14, Week 20, Week 26, Week 28, Week 34, Week 40, Week 42, Week 48 and Week 56/PD. The Screening results will serve as the Baseline value.
- Results of daily Bristol Stool Form Scale beginning at Baseline through Week 56/PD.
- Results of 11-point Abdominal Pain Rating Scale beginning at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.

- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.
- Serological biomarkers/mRNA at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Stool samples for analysis of fecal calprotectin during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Stool samples for microbiota metagenomic analyses during Screening, at Week 4, Week 12, Week 26, and Week 56/PD. The stool samples should be taken before starting bowel preparations for endoscopy.
- Endoscopic evaluations, eligibility confirmed by central reader, will be done at Screening, Week 12, and Week 56/PD.
- An optional pharmacogenetic sample should be drawn at Baseline and Week 12.

Throughout the study, subjects will only be allowed to change the dosage of CD-specific concomitant medications as specified below:

- At Week 4, subjects who are taking corticosteroid therapy at Baseline will have their corticosteroid therapy tapered according to a tapering schedule specified in the clinical study protocol. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the Study Designated Physician (SDP) should be consulted for evaluation and approval.
- Subjects taking corticosteroids at Baseline who have a loss of satisfactory clinical response per the Investigator's judgment after the steroid taper has been initiated may have their corticosteroid dose increased per the Investigator's discretion during the study. Subjects in whom the maximum steroid dose equivalent exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., will be considered non-responders for categorical

endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.

- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.

The study was designed to enroll 500 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.

Re-Screening

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. All screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion and none of the exclusion criteria 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 purified protein derivative (PPD) test (or equivalent), or Interferon Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T SPOT TB test) chest x-ray (if applicable) and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed. If an endoscopy was performed, this will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 45 days have passed between the endoscopy date and the Baseline date. As appropriate, sites are encouraged to contact the AbbVie Study Designated Physician (SDP) to confirm if subjects should or should not be re-screened.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have a Premature Discontinuation Visit. All subjects who discontinue from the study prematurely 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 adverse events (AEs). The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Males and females ≥ 18 and ≤ 75 years of age at Baseline.
2. Diagnosis of colonic, ileocolonic, or ileal Crohn's disease for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before Baseline with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Simplified Endoscopic Score for Crohn's Disease (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader.
4. Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450 at Baseline despite concurrent or prior treatment with a full and adequate course, in the opinion of the Investigator, of at least one of the following (oral corticosteroids and/or immunosuppressants or both as defined below):
    - Subject taking oral corticosteroids, excluding budesonide:
        - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
            - For subjects with a dose > 10 and ≤ 40 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 and the duration of the current steroid course has been at least 14 days prior to Baseline.
- Subject 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 and the duration of the current steroid course has been at least 14 days prior to Baseline.

    or,
- At least a consecutive 42-day course of azathioprine, 6-MP, or injectable MTX prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of at least 230 pmol/8 × 10^8 RBC to clarify a therapeutic level was achieved on the current dosing regimen 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.

    Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.

    or
- Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability, see Section 10.1.

5. Subject may be included if they have previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD-related symptoms) or intolerance (in the opinion of the Investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. Subject has a negative TB Screening Assessment (including a PPD test or QuantiFERON TB Gold test [or equivalent]) and negative chest x-ray (CXR – PA and lateral view) at Screening. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti TB prophylaxis, prior to Baseline.
7. 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 which result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
    - Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone releasing system (IUS)
    - Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
    - Vasectomized partner

- Hormonal contraceptives for at least 90 days prior to study drug administration.

Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol 0.5 mg are not considered adequate.

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

Criteria	Rationale
1	In accordance with good clinical practice (GCP)
2 – 9	In order to select the appropriate subject population with a disease status representative of the target population for evaluation.
10	In order to select subjects who will comply with study procedures for adequate evaluation.

5.2.2 Exclusion Criteria

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.
2. Subject on azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who:
   - Has not been on these medications for at least 42 days prior to Baseline; or
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued these medications within 14 days of Baseline.
3. Subject on oral aminosalicylates who:

- Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
- Has discontinued use of aminosalicylates within 14 days of Baseline.

4. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide > 9 mg/day; or
   - Subject taking an oral corticosteroid (excluding budesonide):
     - dose > 10 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose > 10 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent, but has **not** been on a stable dose for at least 10 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline, or
   - Subject taking budesonide:
     - dose ≥ 6 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose ≥ 6 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose < 6 mg/day dose but has **not** been on a stable dose of at least 10 days prior to Baseline; or
     - dose < 6 mg/day but the current course has **not** been at least 14 days in duration prior to Baseline; or

   Has been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of inhalers.
5. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
6. Subject who has had surgical bowel resections within the past 6 months or is planning any resection at any time point while enrolled in the study.
7. Subject with a symptomatic bowel stricture.

8. Subject with an abdominal or peri-anal abscess.
9. Subject with an ostomy or ileoanal pouch.
10. Subject who has 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. Prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy (PML), including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab [Raptiva®]). Prior exposure to any anti-TNF agent other than infliximab (including etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).
13. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to the Baseline, whichever is longer.
14. Subject who previously received treated with adalimumab or previously participated in an adalimumab clinical study.
15. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 60 days prior to Baseline.
16. Subject who previously received stem cell transplantation.
17. Subject who previously received fecal microbial transplantation.
18. Subject that received non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days prior to Screening and during the Screening visit, except low-dose aspirin for prevention of heart attacks, unstable angina or transient ischemic attacks or topical NSAIDs.

19. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives for non-Crohn's disease related infections within 14 days prior to the Baseline Visit.

20. Subjects on Crohn's disease related antibiotics that have not been on stable doses for at least 4 weeks prior to Baseline. Subjects on Crohn's disease related antibiotics that have discontinued these medications within 4 weeks of Baseline are excluded.

21. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.

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

23. Screening laboratory and other analyses show any of the following abnormal results:

    - AST, ALT > 1.75 × 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.

24. Known hypersensitivity to adalimumab or its excipients.

25. Subject who has previously used infliximab:

    - and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction;

      or

    - who used infliximab within 56 days of Baseline.

26. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.

27. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).

28. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

29. Subjects with a positive result for the Hepatitis B surface antigen (HBs Ag) will be excluded. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab* (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

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

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

        * For HBs Ab test results, a (–) result is equivalent to nonreactive and a (+) result is equivalent to reactive.

30. Chronic recurring infections.

31. Subject with active TB.

32. Subject with latent TB infection unless there is evidence the subject initiated and completed a minimum of 2 weeks of an ongoing TB prophylaxis or has documented completion of a full course of anti-TB prophylaxis, prior to Baseline.

33. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study.

34. Subject with a previous history of dysplasia of the gastrointestinal tract, or found to have dysplasia in any biopsy performed during the Screening endoscopy or endoscopy performed within 45 days before Baseline.
35. Positive pregnancy test at Screening (serum) or Baseline (urine).
36. Female subjects who are breastfeeding or considering becoming pregnant during the study.
37. History of clinically significant drug or alcohol abuse in the last 12 months.
38. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
39. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
40. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Criteria	Rationale
1	To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results.
2 – 5	To exclude subjects who have not been treated with conventional therapies.
19 – 20, 22, 24 – 36, 39	To reduce the risk to subjects or others and/or to exclude underlying conditions that would compromise the subject's safety.
40	To maintain the integrity of other aspects of study conduct, including, subject sampling, treatment procedures, etc.
6 – 10, 11 – 18, 21, 23	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments.
37, 38	To exclude subjects who maybe at increased risk for protocol non-adherence or premature discontinuation.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any non CD-related medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject has received within 30 days prior to Baseline, is receiving at the time of enrollment, or receives during the study, must be recorded 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 electronic case report form (eCRF).

Crohn's disease specific medications (including but not limited to corticosteroids, aminosalicylates, immunosuppressant agents, and CD-related antibiotics) that the subject has received within 90 days of Baseline should be recorded on the appropriate page of the eCRF and should include the dates of administration and dosages. Antibiotics taken for any reason other than Crohn's disease within 90 days of Baseline should be recorded on the appropriate page of the eCRF and should include the reason for use, dates of administration and dosages.

Subjects who failed to respond to corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) within the past 1 year require a confirmed documentation of failure. The dates (start and end dates) of the most recent course of treatment and the maximum daily dosage of the most recent course of treatment and reasons for discontinuation is to be recorded in the appropriate eCRF. In addition the highest known dose taken within the past 1 year will be recorded. For subjects who were intolerant to treatment with corticosteroids or immunosuppressants (azathioprine, 6-MP or MTX) within the past 5 years confirmed documentation of intolerance is required. The highest known dose taken will be recorded in appropriate eCRF.

Subjects who previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD related symptoms) or intolerance (in the opinion of the investigator

therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent will have the highest known dose taken recorded in the appropriate eCRF (Appendix K).

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.

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

5.2.3.2 Concomitant Therapy

Doses of immunosuppressants (including but not limited to) azathioprine, 6-MP, and methotrexate and aminosalicylates taken at Baseline will be continued. Doses must remain stable throughout the duration of the study. Doses may be decreased or terminated in the event of treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the investigator.

Doses of Crohn's disease related antibiotics taken at Baseline will be continued. Change in dose of Crohn's disease related antibiotics during the study will not be allowed except for treatment related toxicities or concerns about development of antibiotic resistance. Newly prescribed CD related antibiotics is not allowed during the study.

Doses of corticosteroids taken at Baseline, as outlined in inclusion criterion 4 in Section 5.2.1, will be continued. Subjects are not allowed 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 who are taking corticosteroid therapy at Baseline will have their corticosteroid therapy tapered according to a tapering schedule specified below and in Section 5.3.1.1.

If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the SDP should be consulted for evaluation and approval.

A proposed regimen to taper prednisone dose starts with a weekly decrease by 5 mg/day prednisone (or equivalent) for doses > 10 mg/day of prednisone (or equivalent) until a 10 mg/day (or equivalent) dose is reached, then a weekly decrease by 2.5 mg/day (or equivalent) until discontinuation. A proposed regimen to taper budesonide dose starts with a weekly decrease by 3 mg/day budesonide until discontinuation.

Subjects taking corticosteroids at Baseline who have a loss of satisfactory clinical response per the Investigator's judgment after the steroid taper has been initiated may have their corticosteroid dose increased per the Investigator's discretion during the study. Subjects in whom the maximum equivalent steroid dose exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population. In addition, subjects in whom the CD-related corticosteroids that were not being taken at Baseline and are initiated during the study will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.

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

Subjects who enter the study on probiotics may continue this therapy provided doses remain stable from Baseline throughout the duration of the study.

Subjects in whom the following CD-related medications (oral or rectal aminosalicylates, thiopurines and MTX) that were not being taken at Baseline and are initiated during the study or who have dosages of these medications increased to greater than the dose taken at Baseline is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Changes in all concomitant medications will be assessed at each study visit from Baseline (Week 0) through Week 56/PD Visits. Any changes will be documented in the source documents and captured on the appropriate eCRF page.

The AbbVie Study Designated Physician 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:
  - Etanercept (Enbrel®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Efalizumab (Raptiva®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Infliximab (Remicade®);
  - Certolizumab pegol (Cimzia®);
  - Golimumab (Simponi®);
  - Vedolizumab (Entyvio®).

- Tofacitinib (Xeljanz®)
- NSAIDs (excluding low-dose aspirin for prevention of heart attacks, unstable angina or transient ischemic attacks and topical NSAIDs).
- Live vaccines (during the study and for 70 days after the last dose of study drug).
- Cyclosporine, tacrolimus, or mycophenolate mofetil (within 60 days prior to Baseline and during the study).
- Recreational or medical marijuana use 14 day prior to Baseline or during the study.

Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy, is prohibited within 14 days prior to Screening endoscopy, during the remainder of 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.

Investigational drugs of a chemical or biologic nature are prohibited within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline and during the study.

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

5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in 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 3. Study Activities

Activity	Screening Period (30 Days)[a]	12-Week Double-Blind Induction Study						44-Week Double-Blind Maintenance Study									Unscheduled Visit[v]	70-Day Follow-Up[t]
	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 (Re-Randomization)	Week 14	Week 20	Week 26	Week 28	Week 34	Week 40	Week 42	Week 48	Week 56/ Premature Discontinuation		
Informed Consent	X																	
Inclusion/Exclusion[b]	X	X																
Medical/Surgery History[b]	X	X																
Previous and Concomitant Medication[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Endoscopy[d]	X						X									X		
Physical Examination[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TB Screening[f]	X																	
Chest X-Ray[g]	X																	
ECG[h]	X																	
Chemistry and Hematology[i]	X	X	X	X		X	X			X			X			X	X	
Urinalysis[i,j]	X	X	X	X	X	X	X			X			X			X	X	
Pregnancy Tests[k]	X[k]	X					X									X		
Hepatitis B Screen and HIV[l]	X																	

Table 3. Study Activities (Continued)

Activity	Screening Period (30 Days)[a]	12-Week Double-Blind Induction Study						44-Week Double-Blind Maintenance Study									Unscheduled Visit[v]	70-Day Follow-Up[t]
	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 (Re-Randomization)	Week 14	Week 20	Week 26	Week 28	Week 34	Week 40	Week 42	Week 48	Week 56/ Premature Discontinuation		
hs-CRP	X		X	X	X	X	X			X			X			X	X	
C. difficile toxin	X																	
Antinuclear antibody (ANA)/Anti-double-stranded DNA (anti dsDNA)[m]	X																	
Stool Sample (microbiota metagenomic analyses and fecal calprotectin)[n]	X			X			X			X			X			X		
Human Antichimeric Antibodies (HACA)/Infliximab Concentrations		X																
Adalimumab Concentration[o]		X	X	X	X	X	X			X			X			X	X	
AAA Concentration[o]		X		X			X			X			X			X	X	
Pharmacogenetic Marker[p]		X					X											
Serological Biomarkers/mRNA		X	X	X		X	X			X			X			X		

Table 3. Study Activities (Continued)

Activity	Screening Period (30 Days)[a]	12-Week Double-Blind Induction Study						44-Week Double-Blind Maintenance Study									Unscheduled Visit[v]	70-Day Follow-Up[t]
	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 (Re-Randomization)	Week 14	Week 20	Week 26	Week 28	Week 34	Week 40	Week 42	Week 48	Week 56/ Premature Discontinuation		
Crohn's Disease Activity Index (CDAI) CDAI components "Number of liquid or very soft stools" and "Abdominal pain" (Stool [liquid/soft] Frequency + Abdominal Pain Score; SFPS)	X	X[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SES-CD Score	X						X									X		
Inflammatory Bowel disease Questionnaire (IBDQ)		X		X		X	X			X			X			X		
European Quality of Life 5 dimensions (EQ-5D)		X		X		X	X			X			X			X		
Work Productivity and Impairment Questionnaire (WPAI)		X		X		X	X			X			X			X		
Abdominal Pain Rating Scale		X	X	X	X	X	X			X			X			X		
Corticosteroid Taper[q]				X	X	X	X	X										
Monitor Adverse Events[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/Administration[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

Table 3. Study Activities (Continued)

Activity	Screening Period (30 Days)[a]	12-Week Double-Blind Induction Study						44-Week Double-Blind Maintenance Study									Unscheduled Visit[v]	70-Day Follow-Up[t]
	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 (Re-Randomization)	Week 14	Week 20	Week 26	Week 28	Week 34	Week 40	Week 42	Week 48	Week 56/ Premature Discontinuation		
Dispense Subject Diary	X																	
Subject Diary Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intestinal Biopsies[p]	X						X									X		

a. The Screening period will be a minimum of 7 days for CDAI calculation. The CDAI calculated at Screening will serve as the Baseline CDAI. Baseline visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around all study visits.

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

c. Height will be measured at Screening only (with shoes off, and then adding 1 inch or 2.5cm).

d. An ileocolonoscopy will be performed during Screening or one performed within 45 days before Baseline, Week 12, and at Week 56/PD. A biopsy will be performed at Screening, Week 12, and Week 56/PD if a suspicious lesion or suspected malignancy, in the assessment of the Investigator, is observed, and evaluated by the local pathologist. Site staff should schedule the Week 12 Endoscopy during the Baseline visit, if possible. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available, a diagnostic biopsy from the most affected observed area of the ileum/colon must be performed during the Screening endoscopy and evaluated by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to evaluate suspicious lesions and to rule out malignancy may be taken during any study endoscopy per the Investigator's discretion and evaluated by the local pathologist.

Table 3. Study Activities (Continued)

e. Physical examination performed at Screening, Week 12 and Week 56/Premature Discontinuation Visits are full physical examinations which must include an assessment of extra-intestinal manifestations (EIMs) and a count of the number of cutaneous fistulas. Physical examinations at all other visits are symptom based and must include a count of the number of cutaneous fistulas.

f. Subjects with negative PPD test and/or QuantiFERON-TB Gold test within 90 days of Screening will not require a repeat skin test, if documentation is available. PPD skin test is to be read 48 to 72 hours after placement.

g. Chest x-ray includes posterior-anterior (PA) **and** lateral views. Subjects with normal chest x-ray within 3 months of Screening would not require a repeat chest x-ray, if documentation is available.

h. Subjects with normal ECG within 90 days of Screening would not require a repeat ECG, if documentation is available.

i. Lab assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

j. Dipstick urinalysis will be completed by the sites at all required visits. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal. Further explanations of these tests are provided in the laboratory manual.

k. Serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy test will be performed locally at Baseline Visit, and at the Week 12 and Week 56/PD for all women of child-bearing 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.

l. 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. Please refer to hepatitis procedures for details on testing requirements. If required by country regulatory authorities to confirm eligibility, subjects will be tested for HIV and documented that the test has been performed. This testing is to be done at a local laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

m. Anti-dsDNA performed if ANA result is positive.

n. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit (supplies will be provided at the time points indicated). The stool from which these samples are prepared should be scored using the Bristol stool chart by ePRO. All stool samples for metagenomic analysis should be collected before any bowel preparation for endoscopy is started and should be returned to the site within 3 days of collection.

   Note: The Screening stool sample may be taken anytime during the Screening period but should be collected prior to any bowel prep.

o. Blood samples for the measurement of adalimumab and AAA concentrations will be collected prior to dosing. Testing of the adalimumab and AAA concentrations must not be performed locally. All pharmacokinetic results will remain blinded to the investigator, study site personnel and the subject throughout the study.

Table 3. Study Activities (Continued)

p. Pharmacogenetic Marker and intestinal biopsy samples are optional. Separate consents must be signed prior to the sample draw. If the pharmacogenetic sample is not collected at Baseline, preferably it should be collected at the next study visit.

q. Subject will begin corticosteroid taper at Week 4. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the SDP should be consulted for evaluation and approval.

r. Collection of SAEs begins the day the subject signs the informed consent.

s. Administration of drug will be performed after all assessments and examinations scheduled for that day have been completed.

t. Subjects will be contacted 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects that continue on adalimumab therapy after the end of study participation.

u. The Screening results of the SFPS will serve as the Baseline value.

v. Visits for dispensing new study drug in case of temperature excursion, loss or damage are not considered an Unscheduled Visit. In addition, visits to retest a lab will not be considered an Unscheduled Visit. Unscheduled Visits according to this table are for purposes when the subject is coming in for a visit for evaluation, assessment and potential dose escalation.

5.3.1.1 Study Procedures

The following study procedures are identical for the Induction Study (Weeks 0 – 12) and the Maintenance Study (Weeks 12 – 56). The study procedures outlined in Table 3 are discussed in detail in this section, with the exception of drug concentration measurements and antibody measurements (discussed in Section 5.3.2), pharmacogenetic and serologic marker/mRNA samples (discussed in Section 5.3.1.2 and Section 5.3.6.2 respectively), pharmacokinetics (discussed in Section 5.3.2) and the collection of adverse event (AE) information (discussed in Section 6.1.4). All study data will be recorded in source documents and on the appropriate eCRFs.

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. Consent will be required for any optional testing.

Inclusion/Exclusion Criteria

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

Medical, Surgical, and Medication History

A complete medical and surgical history, as well as a 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 Visit to ensure that the subject still qualifies.

The location of the subject's Crohn's disease should be recorded in the source documents and on the appropriate eCRFs (anal, perianal, rectum, gastroduodenal, ileum, colon,

and/or jejunum). History should also include onset date, and history of complications related to the disease.

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

A detailed medical history with respect to Loss of Response and/or Intolerance to infliximab must be documented in the subject's source documents. Documentation must include the investigator's judgment based on the conditions defined in Appendix K.

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.

Physical Examination

A full physical examination will be performed at Screening, Week 12 and Week 56/Premature Discontinuation Visits and must include an assessment of extra-intestinal manifestations (EIMs) and a count of the number of cutaneous fistulas as in Table 3. All other visits are symptom based but must include a count of the number of cutaneous fistulas. A count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam. Fistulas will be classified as abdominal or perianal/anal. Physical exam abnormalities noted by the investigator at Baseline (including fistulas and fissures) will be recorded in the subject's medical history.

Abnormalities noted after the Baseline visit will be evaluated and documented by the investigator as to whether they are AEs.

Additionally physical examination findings that are related to or part of each subject's medical history will be captured on the appropriate medical history eCRFs.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, body weight, and body temperature will be obtained at each visit. Blood pressure, pulse rate and respiratory rate should be performed before blood draws are performed. Height will be measured at the Screening Visit only (with shoes off, and then adding 1 inch or 2.5 cm). 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 3. 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 CRA and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol required documentation is available. If there are other findings that are clinically significant, the Principal Investigator must contact the 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 chest x-ray within 90 days of Screening, provided all protocol required documentation is available at the site (as outlined below).

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

In the assessment of the chest x-ray, a radiologist must note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. The CXR reports require the signature of both the radiologist who read the films and the Principal Investigator. If it is the site's policy that the radiologist does not sign the final report, the report must include the date of the procedure, the name of the interpreting radiologist and at a minimum must be signed and dated by the Principal Investigator.

TB Screening

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or a Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed during the Screening Period for all subjects including those with a prior history of BCG administration. If a subject had a negative PPD or IGRA test within 90 days prior to Screening, and all protocol required documentation is available, this test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases must be discussed with the AbbVie SDP.

For the PPD test:

The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours (or according to manufacturer's guide) after placement when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The induration must be recorded in mm not as positive or negative. The absence of induration should be recorded as "0 mm," not "negative." *(If required by specific countries a two-step test may be performed per local guidelines. The result of the second test should be recorded. An induration of 5 mm or greater will be considered as PPD positive.)*

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

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

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

If the PPD or the IGRA test is positive or the subject has a CXR indicative of latent TB, the subject will be required to initiate and have taken at least 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of Center for Disease Control (CDC) recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy.

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

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

Subjects should be screened for TB using either PPD or IGRA. In the event both a PPD test and an IGRA test are performed, if either one is positive, the subject will be

considered to be positive and should initiate TB prophylaxis. If the IGRA test is indeterminate, the site should repeat the test. If the second IGRA test is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis. If the IGRA test is indeterminate, the site should repeat the test with another blood sample or perform a PPD test. If the second IGRA test or PPD is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis.

Prior, ongoing and newly initiated TB prophylactic treatment should be captured on the concomitant medications page in the eCRF and in the source documents. Known history of latent/active TB should be captured on the medical history eCRF page.

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

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of the PPD skin test or the IGRA test and the chest x-ray and provide his/her opinion about the eligibility of each subject to be enrolled to the study. This opinion must be documented in writing in the subject's source documents.
- All subjects with a positive PPD or IGRA test need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie SDP and all such subjects need to receive prophylaxis for latent TB. Under no circumstances can a subject with a positive PPD or IGRA test result and no prior history of treatment for active or latent TB be allowed into this trial.

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 12, and Week 56/PD, subjects of

childbearing potential will have a urine pregnancy test performed locally by designated study personnel. 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. 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 Study Visit (PD) performed locally by designated study personnel.

Hepatitis B Testing

All subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening. A positive result for the Hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab* (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

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

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

* For HBs Ab test results, a (–) result for HBs Ab is equivalent to nonreactive and a (+) result is equivalent to reactive.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 4. Blood draws should be performed after efficacy assessments and questionnaires (CDAI, IBDQ, etc.), vital sign determinations are obtained and before study drug administration during a visit.

Chemistry/hematology and urinalysis assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

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.

If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to the Human Immunodeficiency Virus (HIV) at Screening and documented that the test has been performed. This testing is to be done at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

Table 4. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis***
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/alanine transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase/aspartate 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
		Stool Samples Collected
		C. difficile toxin Fecal calprotectin Microbiota metagenomic analyses
Additional Blood Samples Collected		
High-Sensitivity C-Reactive Protein (hs-CRP) Antinuclear antibody (ANA) Anti–double-stranded DNA (anti-dsDNA) – *if ANA positive* β-HCG HBV Pharmacokinetic Pharmacogenetic and intestinal biopsies (optional) mRNA HACA Infliximab Serologic Biomarkers HIV, if applicable (testing to be conducted at local lab)		

* 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.

Urinalysis

Dipstick urinalysis will be completed by the sites at all required visits as listed in Table 3. Microscopic urinalysis will be performed by the central laboratory in the event the

dipstick UA results show protein, ketones or blood greater than negative or glucose greater than normal.

Other Laboratory Assessments

ANA/anti-dsDNA

Blood samples for antinuclear antibody (ANA) will be obtained per Table 3. Anti-double-stranded DNA (anti-dsDNA) assessments will be performed if ANA is positive.

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

hs-CRP

Blood samples for high-sensitivity C-Reactive Protein (hs-CRP) will be obtained per Table 3. The Screening hs-CRP will serve as the Baseline value. The hs-CRP results in the Induction Study starting from Baseline to Week 8 will remain blinded to Investigator, study site personnel and the subject. The hs-CRP results in the Maintenance Study starting at Week 12 to Week 56 will be unblinded to the Investigator, study site personnel and the subject.

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

Stool Samples Collected

Fecal Calprotectin

Fecal calprotectin will be performed for all subjects as indicated in Table 3. If subjects are unable to provide a sample at the site visit, subjects will be sent home with a stool sample supply kit and the site will give instructions to assist with collection procedures. The fecal calprotectin sample collected during the Screening Period will be used as the

baseline. All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection.

The fecal calprotectin results will remain blinded to Investigator, study site personnel and the subject throughout the study.

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.

Microbiota Metagenomic Analysis

An additional stool microbiota metagenomic analyses will be performed as indicated in Table 3. Subjects will be asked to provide a stool sample at the visit, if possible. Or, subjects will be sent home with stool sample supplies and the site will give instructions with collection procedures. At Screening, Week 12, and Week 56/PD, the stool sample should be collected prior to the bowel preparation for endoscopy has started (if possible) and returned to the site within 3 days of collection. A central laboratory(s) will be utilized to process these laboratory tests.

Where allowed by local requirements at the time of the stool sample collection, any remaining stool could be used for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or development of adverse events. These samples may also be used for the development of

diagnostic tests. Results of exploratory analyses, if any, will not be reported with the study summary. AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for no longer than 20 years after completion of the study (where allowed by local requirements) for possible future research.

Crohn's Disease Activity Index (CDAI)

A CDAI score will be calculated from a subject diary, physical exam, and appropriate laboratory values at all study visits beginning at Screening. The Screening period will be a minimum of 7 days to calculate the CDAI score. The CDAI calculated at Screening will serve as the Baseline CDAI.

Beginning with the Week 2 through Week 56 visits and including unscheduled visits, the CDAI scores must be calculated using a hematocrit value from the preceding visit laboratory work.

CDAI at Visit	HCT Value Utilized
Week 2	Baseline
Week 4	Week 2
Week 6	Week 4
Week 8	Week 4
Week 12	Week 8
Week 26	Week 12
Week 40	Week 26
Week 56	Week 40

For calculating CDAI at Screening through Week 56/Premature Discontinuation, to answer questions one (1) through three (3), entries from the 7 days prior to the visit should be used as recorded by the subject from the diary.

Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier

diary entries will be used accordingly in order to provide the most recent data for 7 days prior to the respective study 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 on the CDAI and calculated into the CDAI score.

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 H, 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.

If the body weight obtained at the time of assessment is not captured in kilograms (kg), then when converting into kg, 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 and 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 score is in Appendix H.

Outcomes and Questionnaires

- IBDQ – Inflammatory Bowel disease Questionnaire (IBDQ) will be completed at the time points indicated in Table 3 (Appendix E).
- WPAI – Work Productivity and impairment Questionnaire will be completed at the time points indicated in Table 3. The data in the subject-completed questionnaire will be transferred to the appropriate eCRF (Electronic Case Report Form) by the site personnel at each study visit (Appendix C).
- EQ-5D – A standardized questionnaire for use as a measure of health outcome (Appendix D).
- Abdominal Pain Rating Scale (Appendix F).
- Bristol Stool Form Scale (Appendix L).
- SES-CD Scoring – Simplified endoscopic score for Crohn's disease – Investigator should complete all components of the SES-CD scoring sheet at the time points indicated in Table 3 (Appendix M).

Corticosteroid Taper

At Week 4, subjects who are on prednisone (or equivalent) or budesonide will taper their dose according to the following regimen or a regimen at the investigator's discretion. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the SDP should be consulted for evaluation and approval.

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

If the subject should experience a loss of satisfactory clinical response in the opinion of the Investigator, the subject may have his/her corticosteroid dose increased per the investigator's discretion up to and beyond the dose used at Baseline. Subjects may not be on both oral budesonide and oral prednisone (or equivalent) simultaneously.

Subject Diary

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

The dosing records will be reviewed and verified for compliance at each visit by the research personnel at the study center and reinforced if necessary. All relevant dosing information will be retained by the study coordinator and transcribed 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 either site medical staff or the subjects or designee (friend, family member or health care professional) during the first visit. The subject or a designated family member or friend will be trained to administer the SC injections of adalimumab. Detailed instructions and training for the administration of adalimumab are provided in Appendix G.

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.

Study drug kits are assigned by the IVRS/IWRS following the subjects randomized treatment schedule.

The Induction Study begins with the first four doses of study drug being administered on site the same day at the Baseline Visit. At the Baseline and Week 2 visits, the IVR will have to be called twice. The first call to the IVR will determine the first two kits to be administered to the subject during the visit. Site staff will need to contact the IVR system a second time to obtain the additional two kits which will be provided to the subject to take home. For Induction and Maintenance Studies, the site staff will remind the subject to take the syringes in the correct order per kit before opening a new kit, when applicable. The IVR will be contacted once at all remaining on-site visits to receive the correct study drug kit(s). The first syringe will be administered at the site and the remaining kits containing syringes will be sent home with the subject. Subjects must be reminded to take the syringes in the assigned kits in the order dispensed by the IVR system.

Subjects should administer study drug on the same day of the week. The dosing dates for all doses of study drug should be calculated from the Baseline Visit date. A ± 3-day window is allowable for scheduled study dosing dates. For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the ± 3-day window, please contact the 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 appropriate therapy initiated. 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, sharp containers and empty boxes at each visit for accountability.

Bristol Stool Assessment

Subjects will rate their stool consistency on a daily basis. The subject should report the type which is most representative for that day according to the Bristol Stool Chart (Appendix L). The Bristol Stool Chart defines 7 types of stool which may be seen in normal and abnormal bowel movements.

Endoscopy

An endoscopy will be performed on the following visits:

- During Screening*
- Week 12
- Week 56/Premature Discontinuation if PD occurs after Week 26

It is expected all subjects will have a Week 12 and 56/PD Endoscopy. Site staff should schedule the Week 12 Endoscopy during the Baseline visit, if possible. For subjects that PD, the site should attempt to reschedule the Endoscopy prior to the discontinuation visit.

*An endoscopy performed before the Screening visit, may be used as the Screening endoscopy, with the approval of the AbbVie Study Designated Physician, if the following conditions are met:

1. biopsy confirmation of the diagnosis is available according to section "Biopsy During Endoscopy" below.
2. the endoscopy took place within 45 days before Baseline Visit.
3. the endoscopy was performed and recorded in a video format as the endoscopic eligibility will be determined by the central reviewers. The same endoscopist, where possible, should perform all endoscopies.

All ileocolonoscopies should be performed and recorded in a video format during the Screening Period or endoscopy performed within 45 days before Baseline and the

Week 56/PD visit. Sites should also perform an SES-CD assessment and record findings on the provided SES-CD score sheet, refer to Appendix M. The findings should be entered in the appropriate eCRF. Videos from Screening endoscopies from subjects the Investigator believes are eligible for the trial (i.e., subjects with an SES-CD ≥ 6, excluding the presence of narrowing component, (or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum), and all Week 12 and Week 56/PD endoscopies conducted will undergo central review. Two primary central reviewers will evaluate the data and provide their score. If the SES-CD scores are discrepant between the two readers, a third central reviewer will review the video and choose between the first and second reviewers' scores. The third reviewer's choice between the reviewers' scores will be considered final. This process will apply to all video endoscopies where the first and second reviewers do not agree. The adjudicator's assessment will be considered final. If, in the opinion of the Investigator, the Screening endoscopy does not indicate the SES-CD criteria confirming study eligibility, the subject should be screen-failed and the video should not be sent for central review. Endoscopic eligibility will be determined by the central reviewers. The same endoscopist, where possible, should perform all endoscopies.

The endoscopy during the Screening Period or endoscopy performed within 45 days before Baseline and Week 56/PD will be used to provide the endoscopy subscores for calculating the Simplified Endoscopic Score (SES-CD) at Screening, Week 12, and Week 56/PD, refer to Appendix M. The SES-CD values provided by the central reader will be used for all endpoint analyses.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available, a diagnostic biopsy from the most affected area of the ileum/colon must be performed during Screening and read by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to evaluate suspicious lesions or to rule out malignancy may be taken per the Investigator's

discretion and evaluated by the local pathologist. If the biopsy sample(s) are obtained during the endoscopy used to determine subject eligibility, it should also be recorded. The biopsy should not interfere with the recording the central reviewers will use for their evaluation.

The signed pathology reports confirming diagnosis and when appropriate, ruling out current dysplasia/malignancy will be monitored by the responsible Clinical Research Associate (CRA) and kept with the subject's source documents onsite. Subjects should not be enrolled if colon dysplasia or malignancy is discovered at Screening endoscopy or endoscopy performed within 45 days before Baseline. If a diagnosis of colon dysplasia or malignancy is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be recorded as an adverse event and the subject should be discontinued from the study.

5.3.1.2 Blood Sample for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected per Table 3 from each subject who consents for pharmacogenetic analyses. If the sample is not drawn at the Baseline visit, preferably it should be drawn at the next study visit. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. Please refer to the laboratory manual for instructions.

Samples will be shipped frozen to the central laboratory and then to AbbVie 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.

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

See Section 5.3.6.1 for the variables of this analysis.

5.3.1.3 Blood Samples for Biomarkers Analysis

Collection of Samples for Serologic Markers

Two 5 mL blood samples for serologic markers analysis will be collected at the time points indicated in Table 3. Please refer to the laboratory manual for specific instructions. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

The frozen serum and plasma samples for Serologic Marker analysis will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. An inventory of the samples included will accompany the package. Arrangements will be made with the central laboratory for the shipment of serologic samples to AbbVie or specified lab for testing.

See Section 5.3.6.2 for the variables of this analysis.

Collection of Samples for mRNA Assays

Two 2.5 mL blood samples for mRNA will be collected at the time points indicated in Table 3. Please refer to the laboratory manual for specific instructions.

The frozen samples for mRNA analysis will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. An inventory of the samples included will accompany the package. Arrangements will be made with the central laboratory for the shipment of samples to AbbVie or specified lab for testing.

5.3.1.4 Collection and Handling of Optional Intestinal Biopsy Samples for Exploratory Research

Subjects will have the option to provide intestinal biopsy samples for exploratory research, where allowed by local requirements. Subjects may participate in the main study even if they decide not to participate in this optional exploratory research.

Exploratory research can improve our understanding of how individuals respond to drugs and our ability to predict which patients would benefit from receiving specific therapies. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor IBD by assessing associations between disease characteristics, outcomes data and biomarkers of interests.

AbbVie (or people or companies working with AbbVie) will store the biomarker exploratory research samples 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) or Inflammatory Bowel Disease and related conditions continues, but for no longer than 20 years after study completion (where allowed by local requirements).

Collection of Optional Intestinal Biopsy Samples for Exploratory Research

During the Screening endoscopy, intestinal biopsy samples are desired from the recto-sigmoid, transverse and left colon. If there is inflammation in any of these 3 colonic segments, use standard biopsy forceps to collect one biopsy from the most inflamed area or the edge of an ulcer if ulcers are present, and one biopsy from a normal area in that segment at least 15 mm away from any inflamed area. If possible collect biopsies from several places in each inflamed segment up to a total of 24 biopsies per subject.

At Week 12 and Week 56 or Premature Discontinuation biopsies from the most inflamed areas are again requested. A biopsy of the edge of an ulcer, if ulceration is present and one biopsy from a normal mucosa in each segment at least 15 mm from any inflamed area and one biopsy in a healed area, if an area showed active disease at baseline can be easily identified.

Samples will be shipped to AbbVie or a designated laboratory for long-term storage. Instructions for the preparation and shipment of the biomarker exploratory research samples will be provided in a laboratory manual.

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 3.

Testing of the adalimumab and AAA concentrations must not be performed locally. All pharmacokinetic results will remain blinded to the investigator, study site personnel and the subject throughout the study.

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. Please refer to the laboratory manual for instructions.

A maximum of 15 samples (not including unscheduled visit sample collections) are planned to be collected per subject for adalimumab (9 samples) and AAA (6 samples) assays. The total number of samples planned will not exceed 2,700 (9 samples × 300 subjects) for the adalimumab assay and 1,800 (6 samples × 300 subjects) for the AAA assay for the entire study.

Some samples might be obtained and stored to analyze for factors contributing to the subject's response to study treatment, in terms of pharmacokinetics, pharmacodynamics, tolerability or safety after the study.

Collection of Samples for Infliximab and HACA Assays

Blood samples for infliximab and HACA assay will be collected at Baseline by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes without gel separator at Baseline. The sample will be obtained immediately prior to dosing. Sufficient blood will be collected to provide approximately two 1 mL serum specimens (one tube for infliximab and one tube for HACA). Please refer to the laboratory manual for instructions.

The total number of samples planned will not exceed 500 (2 samples × 300 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.

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 Co-Primary Variables for Induction Study

- Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 4.
- Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 12.

5.3.3.2 Secondary Variables for Induction Study

Ranked Secondary endpoints:

1. Proportion of subjects with sustained clinical remission (CDAI < 150) at both Weeks 4 and 12.
2. Proportion of subjects with CDAI < 150 at Week 4 and endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 12.
3. Proportion of subjects with clinical remission (CDAI < 150) at Week 12.
4. Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 12 among subjects taking corticosteroids at Baseline.
5. Proportion of subjects with endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 12.
6. Change from Baseline in fecal calprotectin level at Week 4.
7. Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g at Week 4.

8. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g at Week 4.
9. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 12.
10. Proportion of subjects who achieve an SES-CED ≤ 2 at Week 12.
11. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 4.
12. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 12.
13. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 4.
14. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 12.
15. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 12.

All additional efficacy endpoints will be non-ranked.

- Proportion of subjects with clinical response (decrease CDAI ≥ 70 points from Baseline) at each scheduled visit in Induction Study.
- Proportion of subjects with enhanced clinical response (decrease CDAI ≥ 100 points from Baseline) at each scheduled visit in Induction Study.
- Proportion of subjects who discontinue corticosteroid use at each scheduled visit in Induction Study among subject taking corticosteroids at Baseline.
- Proportion of subjects who achieve a composite subtotal score of SFPS < 50 at Week 12 who had an SFPS ≥ 100 at Baseline.
- Proportion of subjects who achieve a composite subtotal score of SFPS < 50 at Week 4 who had an SFPS ≥ 100 at Baseline.

- Proportion of subjects who achieve SES-CD ≤ 3 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12.
- Proportion of subjects with SES-CD = 0 at Week 12.
- Change from Baseline in fecal calprotectin level at each scheduled visit in Induction Study.
- Change from Baseline in hs-CRP at each scheduled visit in Induction Study.
- Change in IBDQ total score and individual IBDQ domain scores (bowel, emotional, social, systemic) from Baseline at each scheduled visit in Induction Study.
- Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Baseline) at each scheduled visit in Induction Study.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) at each scheduled visit in Induction Study.
- Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 4.
- Change in WPAI from Baseline at each scheduled visit in Induction Study.
- Change in EQ-5D from Baseline at each scheduled visit in Induction Study.
- Change in CDAI from Baseline at each scheduled visit in Induction Study.
- Change in SFPS from Baseline at each scheduled visit in Induction Study.
- Change in Abdominal Pain Rating Scale score from Baseline at each scheduled visit in Induction Study.
- Change in Bristol Stool Chart score from Baseline at each scheduled visit in Induction Study.
- Proportion of subjects who achieve Bristol Stool Chart response at each scheduled visit in Induction Study.
- Proportion of subjects who achieve CDAI remission (CDAI < 150) at each visit in Induction Study.
- Proportion of subjects who achieve SFPS remission (SFPS < 50) at each scheduled visit in Induction Study.

- Change in each CDAI component subscore (number of liquid or very soft stools, abdominal pain rating, general well-being, CD related complications, anti-diarrhea use, abdominal mass, hematocrit, body weight) from Baseline at each scheduled visit in Induction Study.
- Time to clinical remission (CDAI < 150) in Induction Study.
- Time to clinical response (CR –70) in Induction Study.
- Time to all cause Hospitalization in Induction Study.
- Time to CD-related Hospitalization in Induction Study.
- Proportion of subjects with no draining fistulas at Week 12 among subjects with draining fistula at Baseline.
- Proportion of subjects in each treatment group with > 50% reduction from Baseline in the number of draining fistulas at Week 12 among subjects with draining fistula at Baseline.
- Resolution of extra-intestinal manifestations over time at each scheduled visit in Induction Study.
- Proportion of subjects with an SES-CD decrease of ≥ 3 points compared to Baseline at Week 12.
- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than baseline) and average daily abdominal pain ≤ 1.0 (and not worse than baseline), at each scheduled visit in Induction Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.
- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline or average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline, at each scheduled visit in Induction Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.

5.3.3.3 Endpoints for Exploratory Maintenance Study

- Proportion of subjects who achieve endoscopic response (SES-CD > 50% from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 56 among subjects with endoscopic response at Week 12

- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic remission at Week 12.
- Proportion of subjects who achieve CDAI < 150 at Week 56 among subjects with CDAI < 150 at Week 12.
- Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 56.
- Proportion of subjects who achieve SES-CD ≤ 4 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 56.
- Proportion of subjects who achieve SES-CD ≤ 2 at Week 56.
- Proportion of subjects with CDAI < 150 at Week 4 and SES-CD ≤ 4 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 56.
- Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 56 among subjects taking corticosteroid at Baseline.
- Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 56.
- Change from Baseline in fecal calprotectin level at Week 56.
- Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g at Week 56.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at Week 56.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least 2 point reduction versus baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 56.
- Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 56.

- Proportion of subjects with clinical response (decrease CDAI ≥ 70 points from Baseline) at each scheduled visit in Maintenance Study.
- Proportion of subjects with enhanced clinical response (decrease CDAI ≥ 100 points from Baseline) at each scheduled visit in Maintenance Study.
- Proportion of subjects who discontinue corticosteroid use at each scheduled visit in Maintenance Study among subjects taking corticosteroid at Baseline.
- Proportion of subjects who achieve a composite subtotal score of SFPS < 50 at Week 56 who had an SFPS ≥ 100 at Baseline.
- Proportion of subjects who achieve SES-CD ≤ 3 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 56.
- Proportion of subjects with SES-CD = 0 at Week 56.
- Change from Baseline in fecal calprotectin level at each scheduled visit in Maintenance Study.
- Change from Baseline in hs-CRP at each scheduled visit in Maintenance Study.
- Change in IBDQ total score and individual IBDQ domain scores (bowel, emotional, social, systemic) from Baseline at each scheduled visit in Maintenance Study.
- Change in WPAI from Baseline at each scheduled visit in Maintenance Study.
- Change in EQ-5D from Baseline at each scheduled visit in Maintenance Study.
- Change in CDAI from Baseline at each scheduled visit in Maintenance Study.
- Change in SFPS from Baseline at each scheduled visit in Maintenance Study.
- Change in Abdominal Pain Rating Scale score from Baseline at each scheduled visit in Maintenance Study.
- Change in Bristol Stool Chart score from Baseline at each scheduled visit in Maintenance Study.
- Proportion of subjects who achieve CDAI remission (CDAI < 150) at each scheduled visit in Maintenance Study.
- Proportion of subjects who achieve SFPS remission (SFPS < 50) at each scheduled visit in Maintenance Study.

- Proportion of subjects with major CD related event (e.g., hospitalization, bowel surgery, abscess drainage) in Maintenance Study.
- Proportion of subjects with no draining fistulas at Week 56 among subjects with draining fistula at Baseline.
- Proportion of subjects in each treatment group with > 50% reduction from Baseline in the number of draining fistulas at Week 56 among subjects with draining fistula at Baseline.
- Resolution of extra-intestinal manifestations at each scheduled visit in Maintenance Study.
- Proportion of subjects with an SES-CD decrease of ≥ 3 points compared to Baseline at Week 56.
- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than baseline) and average daily abdominal pain ≤ 1.0 (and not worse than baseline), at each scheduled visit in Maintenance Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.
- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline or average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline, at each scheduled visit in Maintenance Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.
- Time to dose escalation in Maintenance Study.
- Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Baseline) at each scheduled visit in Maintenance Study.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) at each scheduled visit in Maintenance Study.
- Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at each scheduled visit in Maintenance Study.
- Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at each scheduled visit in Maintenance Study.

- Proportion of subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.

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 throughout the study.

5.3.5 Pharmacokinetic Variables

Blood samples will be collected for measurement of serum adalimumab concentration just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/Premature discontinuation and anti adalimumab antibody (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56/Premature Discontinuation.

Blood samples will also be collected for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.

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.

5.3.6 Pharmacogenetic and Serologic Variables

5.3.6.1 Pharmacogenetic Variables

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

5.3.6.2 Serologic Variables

Samples may be analyzed for plasma and serum proteins, peptides, and non-protein soluble factors such as lipids that may help predict disease behavior and help determine more severe disease phenotypes.

Where allowed by local requirements at the time of the blood draw for biomarkers, serum may be stored for possible future research. Samples will be stored frozen for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or development of adverse events. These samples may also be used for the development of diagnostic tests. Results of exploratory analyses, if any, will not be reported with the study summary. AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. As allowed by local requirements, the samples will be retained for up to 20 years after completion of the study research.

5.3.7 Exploratory Research Variables

Optional intestinal biopsy samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to: nucleic acids, proteins, lipids or metabolites.

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of Inflammatory Bowel Disease or related conditions and/or adalimumab or drugs of similar class. The results from these analyses are exploratory in nature and may not be included with the study report.

The samples may also be used to develop new therapies, research methods or technologies. In addition, samples from this study may be banked for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

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.
- The subject becomes pregnant while on study drug.
- Subject has dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie 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 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

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 that 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

During the randomized double-blind Induction Study, subjects assigned to the higher induction regimen will receive blinded adalimumab 160 mg (4 syringes) at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects will receive 40 mg (1 syringe) eow through Week 12.

Subjects assigned to the standard induction regimen will receive blinded adalimumab 160 mg (4 syringes) at Baseline and matching placebo (4 syringes) at Week 1. Subjects will receive 80 mg (2 syringes) and placebo (2 syringes) at Week 2 and matching placebo (4 syringes) at Week 3. At Week 4, subjects will receive 40 mg (1 syringe) eow through Week 12.

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of the two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen). The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70)

status at Week 12 and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Clinically Adjusted (CA) Regimen:

Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week starting as early as Week 14 if the subject's CDAI is ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit). These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the CA regimen are escalated, they will remain on 40 mg ew dosing.

Therapeutic Drug Monitoring (TDM) Regimen:

At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM will be determined by the dose adjustment criteria table (Table 2). Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.

The duration of the study could be up to 60 weeks which includes a Screening Period of 1 to 4 weeks, ± 3 days which is granted around all study visits, a 12-week double-blind period Induction Study, and a 44-week Maintenance Study. The Screening period may be extended as necessary after consultation and approval with the AbbVie Study Designated Physician (SDP) for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of

availability of screening test results). There will also be a 70-day follow-up phone call for subjects who complete Week 56 or discontinue from the study prematurely.

No dose will be given at the final visit.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 5.

Table 5. 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 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 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 drug 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 G.

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab/placebo pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study 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 on a temperature log to record proper function.

Malfunctions or any temperature excursion lasting longer than 30 minutes must be reported to the Sponsor immediately. Study drug should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS), or alternate system, 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 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 in a 3:2 ratio to receive a higher induction regimen or standard induction regimen.

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of the two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen).

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 directions for the IVRS will be provided to each site. Study drug will be administered at the study visits summarized in Table 3.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in Section 5.5.1.

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

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

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

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personally with direct oversight of the conduct and management of the trial (with the exception of AbbVie's Drug Supply Management Team) the Investigator, study site personnel and the subject will remain blinded to each subject's treatment throughout

the blinded period of the study. The IVRS/IWRS will provide access to blinded subject treatment information in the case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie SDP (see Section 7.0) prior to breaking the blind, as long as it does not compromise subject safety. 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 representatives will dispense study drug only for use by subjects enrolled in the study.

The subject or their qualified designee will administer all doses of study drug. Appropriate site staff will supervise the subject's administration of the study drug at required in-office study visits to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a 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 on a Site Drug Accountability log including date received, the lot number, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug. For this study, unless otherwise prohibited locally, these records will be maintained electronically as part of the IVRS/IWRS system.

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical trial was chosen to demonstrate the efficacy of a higher induction regimen of adalimumab compared to the standard induction regimen. The efficacy time points of Week 4 and Week 12 are comparable to prior studies with adalimumab, specifically Study M02-403, Study M04-691, and Study M05-769. The

study is double-blinded and subjects are randomized to receive a higher induction regimen of adalimumab or a standard induction regimen of adalimumab. After the induction regimens are provided, subjects in both treatment groups will receive blinded adalimumab 40 mg eow until Week 12. Subjects will begin tapering of corticosteroids at Week 4.

No placebo arm is planned since there is well-documented efficacy of adalimumab in CD and because the purpose of this study is to achieve better efficacy than the standard induction regimen in terms of clinical remission and endoscopic improvement. Additionally, since subjects will be required to have failed or been intolerant of standard therapies and have evidence of endoscopic damage confirmed by a central reader, it would be not medically acceptable to deny those patients effective treatment or feasible to enroll patients in the trial when adalimumab is available to be prescribed for CD.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, endoscopy-related and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with Crohn's disease. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

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 evidence of mucosal ulceration.

5.6.4 Selection of Doses in the Study

The use of an induction dose higher than the approved dose of 160/80 mg (Week 0/2) is supported by exposure-efficacy modeling analyses from the pivotal registration Study M02-403 (anti-TNF naïve subjects) and Study M04-691 (anti-TNF experienced subjects).

The goal of the TDM regimen is to attain and maintain serum adalimumab levels above reasonably high concentration levels in subjects for mucosal healing. Since exposure and endoscopic relationships are not currently available for adalimumab, clinical remission was used for the selection of concentration thresholds to be used in the TDM regimen. Based on the PK analyses of adalimumab concentrations in the adult Crohn's disease studies, Studies M02-403, M04-691 and M02-433, no concentration level could be identified as a significant and reliable predictor of remission. Therefore, the TDM regimen will be based on two concentration thresholds in conjunction with clinical response criteria as expected to occur in the clinical setting. About 75% of the subjects, who were in remission at Week 56 in Study M02-433, had serum concentration levels above 5 µg/mL. The lower concentration threshold for the TDM regimen was selected as 5 µg/mL; thus, any subject below 5 µg/mL concentration will be escalated to ew dosing regardless of their CDAI or hs-CRP level. The second threshold was selected as 10 µg/mL, which is similar to the median concentrations (9.4 µg/mL at Week 56) observed in subjects who were in remission. The subjects with concentration above 5 and below 10 µg/mL may be dose escalated based on clinical response as outlined in the table below. The subjects with serum concentration above 10 µg/mL will not be dose escalated.

6.0 Complaints

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

The investigational product in this trial contains both:

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7. 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 AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An 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 (see Section 6.2 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 SAE within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

6.1.2 Adverse Event Severity

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

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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

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

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

6.1.4 Adverse Event Collection Period

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

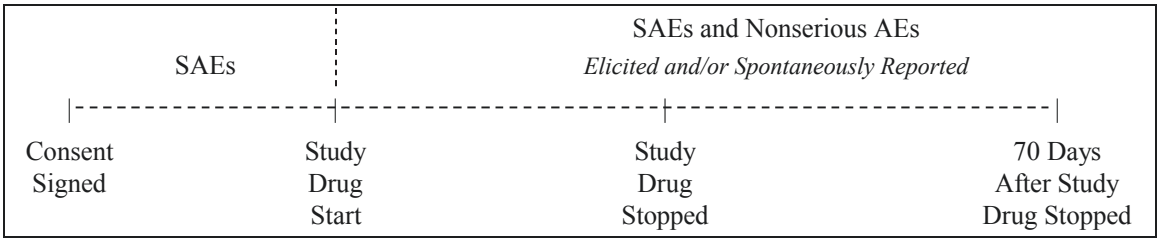
Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects that continue on adalimumab therapy after the end of study participation. These subjects are not required to complete the 70-day follow-up and any new Adverse Events should be reported

through the mechanism used for all post-marketing adverse experiences. The 70-day follow-up phone call will be recorded in source document only and confirmation of the contact will be faxed to AbbVie (Appendix J).

All Adverse Events identified to AbbVie from the 70-day follow-up phone call will be collected as source data to be evaluated and reported (Figure 3). Thus, all SAEs and nonserious AEs as defined by AbbVie, reported during the 70-day follow-up phone call must be captured in the clinical database. The end of trial is the last subject contact, i.e., the 70-day follow-up call.

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

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the investigator will notify the AbbVie Clinical Pharmacovigilance within 24 hours of the site being made aware of the event by entering the serious adverse event or nonserious event of malignancy in patients 30 years of age and younger data into the RAVE® electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in patients 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-case report forms (CRF) and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Immunology Safety Management Team at:

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

Office: [redacted]
Email:

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

Primary Study Designated Physician:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Contact Information:
Office:
Mobile: [redacted]
Email:

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie SDP:

Phone: [redacted]

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

6.1.6 Pregnancy

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

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

Pregnancy in a study subject is not considered an 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 6.0 for definitions). Study drug 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 drug 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, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

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

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 their assigned CRO Clinical Monitor or the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
GPRD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

Alternate Contact:

[redacted]
GPRD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab in achieving clinical remission and endoscopic improvement in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration.

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 at Baseline. ITT subjects will be analyzed as randomized. ITT set is the primary population for the

efficacy analysis for the Induction Study. If there is > 10% difference in number of subjects with actual treatment received and the treatment randomized, a sensitivity analysis for the co-primary endpoints based on the actual treatment received will be performed.

Modified Intent-to-Treat (mITT) set includes all ITT subjects who achieve clinical response (CR-70) at Week 12. The mITT set is the primary population for the efficacy analysis for the Maintenance Study.

The safety set consists of all 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 for Induction Study

The co-primary efficacy variables for Induction Study are proportion of subjects with moderately to severely active CD that have achieved clinical remission, defined as CDAI < 150, at Week 4 and proportion of subjects that have achieved endoscopic response, defined as a decrease > 50% SES-CD from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.

The comparisons between treatment group difference on the two co-primary efficacy variables for Induction Study will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by hs-CRP at Baseline (< 10 and ≥ 10 mg/L), prior infliximab use, and Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline. 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 or SES-CD at Week 12 will be imputed using the non-responder imputation (NRI) approach.

For Week 4 clinical remission, LOCF, OC and multiple imputation methods will be used as sensitivity analyses. For Week 12 endoscopic response, OC will be used as sensitivity analysis.

In addition, as sensitivity analyses, the logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as corticosteroid use at Baseline, IMM use at Baseline, Baseline fecal calprotectin, Baseline SES-CD, and Region (US versus ex-US), will also be performed for the co-primary endpoints.

8.1.4.2 Secondary Efficacy Variables for Induction Study

Secondary efficacy variables are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at 0.050 (2-sided) in ranked endpoint order until the significant level exceeds

0.05. No additional statistically significant treatment differences could be declared after the first ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables.

For categorical ranked and non-ranked secondary endpoints, the difference in proportions of subjects between treatment groups will be analyzed using the CMH test adjusted for stratification variables. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. The non-responder imputation will be used for subjects with missing data at the endpoint evaluated. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses for the primary and ranked secondary endpoints.

Change from Baseline in continuous ranked and non-ranked secondary 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 OC analyses will be performed. The LOCF analysis is considered primary for inferential purposes. In addition, Mixed-Effect Model Repeated Measure (MMRM) will be applied, wherever appropriate, as a sensitivity analysis for the longitudinal continuous endpoints.

8.1.4.3 Efficacy Variables for Maintenance Study

For categorical endpoints, the difference in proportions of subjects between treatment groups will be analyzed using the CMH test adjusted for stratification variables. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. The non-responder imputation will be used for subjects with missing data at the endpoint evaluated. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses for the primary and ranked secondary endpoints.

Change from Baseline in continuous ranked and non-ranked secondary 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 OC analyses will be performed. The LOCF analysis is considered primary for inferential purposes. In addition, Mixed-Effect Model Repeated Measure (MMRM) will be applied, wherever appropriate, as a sensitivity analysis for the longitudinal continuous endpoints.

8.1.5 Statistical Analyses of Safety

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed for both induction and maintenance periods between treatment groups using the safety analysis set.

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 for subjects who do not participate in the OLE or until first dose of study drug in the OLE study if the subject is a completer and is enrolled in the OLE.

Treatment-emergent AEs will be summarized separately for: a) Baseline to Week 12; b) Week 12 to Week 56; c) Baseline to Week 56 (overall study duration). An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 20.1 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.

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)
- Race (white, non-white)
- Baseline fecal calprotectin [≤ median, > median]
- Baseline fecal calprotectin [≤ 250 µg/g, > 250 µg/g]
- Baseline corticosteroid use (YES, NO)
- Baseline immunosuppressants use (YES, NO)
- hs-CRP at Baseline (< 10 and ≥ 10 mg/L)
- hs-CRP at Baseline (≤ median, > median)
- Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline
- Baseline CDAI (≤ median, > median)
- Baseline SES-CD [≤ median, > median]
- Prior infliximab use (YES, NO)
- Weight (≤ median, > median)
- Baseline albumin (≤ median, > median)
- Disease duration (≤ 3 years, > 3 years)
- Disease duration (≤ median, > median)
- Region (US, ex-US)

8.1.7 Interim Analysis

An interim analysis of the primary endpoint and ranked secondary efficacy variables for the Induction Study only as well as safety data collected from Baseline through double-blind Week 12 may be performed after the last subject in ITT population completes the 12-week double-blind Induction Study. A database cut will be performed and any discrepant data will be clarified before the lock. Since this interim analysis is the only and final analysis of the co-primary efficacy endpoints of the Induction Study, multiplicity adjustment is deemed not necessary.

8.1.8 Pharmacokinetic Analyses

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

8.2 Determination of Sample Size

The calculated Week 4 remission rate for higher dose regimen are based on the average of the PK-PD Linear model and E_{max} model and is 56% [(70% [Linear] + 42% [E_{max}]) / 2] for infliximab naïve subjects and 45% [(60% [Linear] + 30% [E_{max}]) / 2] for infliximab experienced subjects. Assuming the ratio in the proposed study of infliximab naïve subjects versus infliximab experienced is 75% versus 25%, respectively, the weighted Week 4 remission rate will be approximately 50% for higher induction dose regimen. For the standard dose regimen, the Week 4 clinical remission rate will be approximately 30%. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 3:2 ratio at Baseline to receive a higher induction adalimumab regimen or standard induction adalimumab regimen during the double-blind period. A sample size of 500 (300 higher dose and 200 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts a ~50% increase in the proportion of subjects with endoscopic response is expected. The observed rate of

endoscopic response in Study M05-769 was 44% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate endoscopic response at Week 12 using the higher induction regimen is 66%. A sample size of 500 subjects (300 higher induction regimen and 200 standard induction regimen) will be adequate to detect at least an 22% treatment difference in endoscopic response rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 99% power at a 0.05 two-sided significance level.

Since the clinical remission at Week 4 endpoint and the endoscopic response at Week 12 endpoint are likely not independent of each other, the power for the co-primary endpoints for the study is expected to be > 98%.

8.3 Randomization Methods

At Baseline, subjects will be randomized 3:2 to one of two double-blinded adalimumab Induction Study regimens (higher induction regimen or standard induction regimen). The randomization will be stratified by hs-CRP at Baseline (< 10 and ≥ 10 mg/L), using Screening hs-CRP values, prior infliximab use, Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline.

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of two double-blinded exploratory treatment regimens (clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen). The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12, and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

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 International Conference on Harmonization (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, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and 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.

Any optional testing will only be performed 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 optional testing is performed. If the subject does not consent to the optional testing, it will not impact the subject's participation in the study.

In the event a subject withdraws consent to participate from the study, stored biomarker and optional samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples not be analyzed. Once AbbVie receives the request, remaining biomarker and/or optional samples will be destroyed. However, if the subject changes his/her consent, and the samples have already been tested, those results will remain as part of the overall research data.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

Case report forms 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 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
- WPAI
- EQ-5D
- Abdominal Pain Rating Scale

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.

10.3 Electronic Patient Reported Outcomes (ePRO)

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

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

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

The ePRO data (Bristol Stool Form scale, number of liquid or very soft stools, use of medications used for endoscopy preparation, dosing information, and general well-being) will be collected electronically via a handheld device into which the patient will record the required pieces of information on a daily basis. The electronic device will be programmed to allow for data entry once per day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, until the generation, receipt and confirmation of the study archive.

10.4 Data Collection Process

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

11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires and Subject Dosing Diary completion, and specimen collection methods.

Sites will be monitored throughout the study and 100% source document verification will be performed.

All data entered in the database will be verified at AbbVie. Any discrepancies will be reviewed and necessary corrections will be made to the eCRF by the site. The data will be reviewed and computer electronic logic checks will be run to identify items such as inconsistent study dates. A manual review of selected line listings will also be performed throughout and at the end of the study.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A review of all laboratory results will be conducted by the AbbVie monitors (or their representatives), the Study Investigator and other appropriate personnel from AbbVie. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

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.

If this protocol or the information gained from the conduct of this study will be made public (disclosed/published), AbbVie will determine the information that is not yet in the public domain and if the disclosure of such information may undermine AbbVie's interests, will remain confidential at the time of disclosure/publication.

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 research that may be done using pharmacogenetic or exploratory research 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 or exploratory research information from this study may be used in scientific publications or presented at medical conventions. 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 or the actual date of follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration
Protocol Date:	27 November 2018

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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4. Allez M, Lemann M, Bonnet J, et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97(4):947-53.
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7. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology. 2012;142(5):1102-11.e2.
8. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60(4):505-12.
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Appendix A. Responsibilities of the Clinical Investigator

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

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

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Statistics
		Bioanalysis
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical

Appendix C. Sample Work Productivity and Activity Impairment Questionnaire: Crohn's Disease V2.0 (WPAI:CD)

Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD)

The following questions ask about the effect of your Crohn's disease on your ability to work and perform regular activities such as physical or emotional problems or symptoms. *Please fill in the blanks or circle a number, as indicated.*

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

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

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

   _____HOURS

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

   _____HOURS

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

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

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

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as

usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.

Consider only how much Crohn's disease affected productivity while you were working.

Crohn's disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your Crohn's disease affect your ability to do your regular daily activities, other than work at a job?
   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.

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

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

CIRCLE A NUMBER

Appendix D. Sample EQ-5D Questionnaires

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking	☐
I have slight problems walking	☐
I have moderate problems walking	☐
I have severe problems walking	☐
I am unable to walk	☐

SELF-CARE

I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

USUAL ACTIVITIES
(e.g., work, study, housework, family or leisure activities)

I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐

PAIN/DISCOMFORT

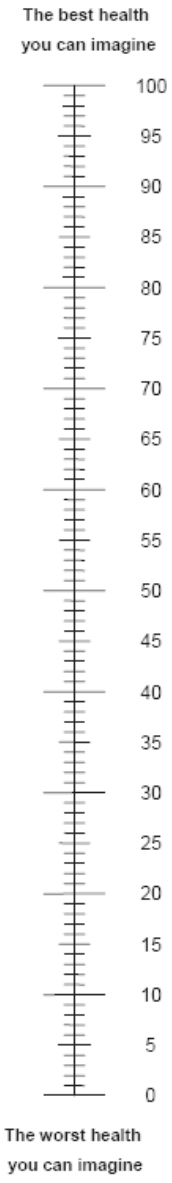
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

ANXIETY/DEPRESSION

I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix E. 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

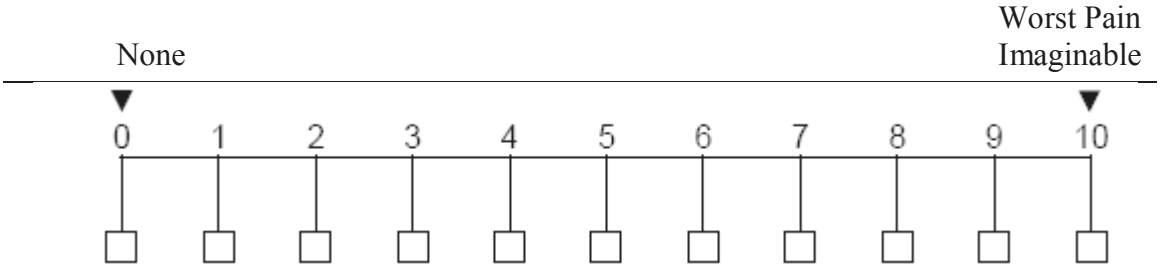
IBDQ

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 F. Abdominal Pain Rating Scale

Please rate your abdominal pain intensity by indicating the number that best describes your abdominal pain on average in the last 24 hours.



0 None – No symptoms.

1 – 3 Mild – The pain is transient and easily tolerated, not requiring any treatment.

4 – 6 Moderate – The pain caused discomfort and interrupted usual activities. Some form of treatment was required.

7 – 9 Severe – The pain caused considerable interference with usual activities and may have been incapacitating, requiring treatment.

10 Worst Imaginable – The pain causes extensive interference with usual activities and is incapacitating, requiring strong analgesics and/or hospitalization.

Appendix G. Injection Instructions – Sample Pre-Filled Syringe

Subject Instructions

0.8 mL dose

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

Protocol M14-115

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 1 you will administer 4 injections (2 kits) at home.
- Week 2 you will receive 4 injections (2 kits) at the clinic.
- Week 3 you will administer 4 injections (2 kits) at home.
- At Weeks 4, 6, 8, 12, 14, 20, 26, 28, 34, 40, 42 and 48 you will receive 1 injection at the clinic.
- At Weeks 10, 13, 15 – 19, 21 – 25, 27, 29 – 33, 35 – 39, 41, 43 – 47, 49 – 55 you will administer 1 injection 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:

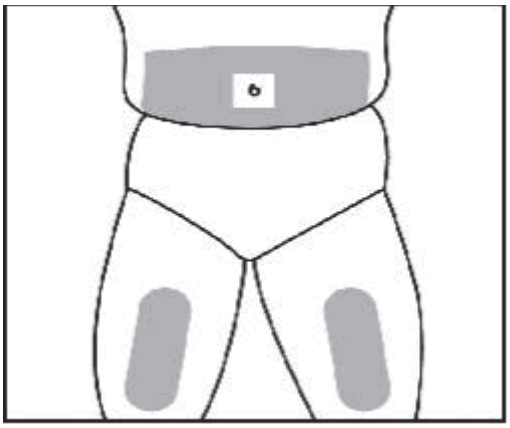
- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

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 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.
- 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 H. Crohn's Disease Activity Index (CDAI)

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	__+__+__+__+__+__+__+__=___ Days: 1 2 3 4 5 6 7 Sum	×	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	__+__+__+__+__+__+__+__=___ Days: 1 2 3 4 5 6 7 Sum	×	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	×	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	×	20	
5. Taking Lomotil/Imodium/ Loperamide/opiates for diarrhea 0 = no, 1 = yes	_____	×	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	×	10	
7. Hematocrit: ___.__	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal If hematocrit > normal, enter "0"	×	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"	×	1	
			Total	

Appendix I. Standard Weights

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard 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		
Standard 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		
Standard 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)	*Standard height is calculated using actual height obtained at screening (without shoes) plus one inch
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

Appendix J. 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 or moved into the OLE study (M14-347).

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 K. Guidelines to Evaluate Loss of Response and Intolerance to Infliximab

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

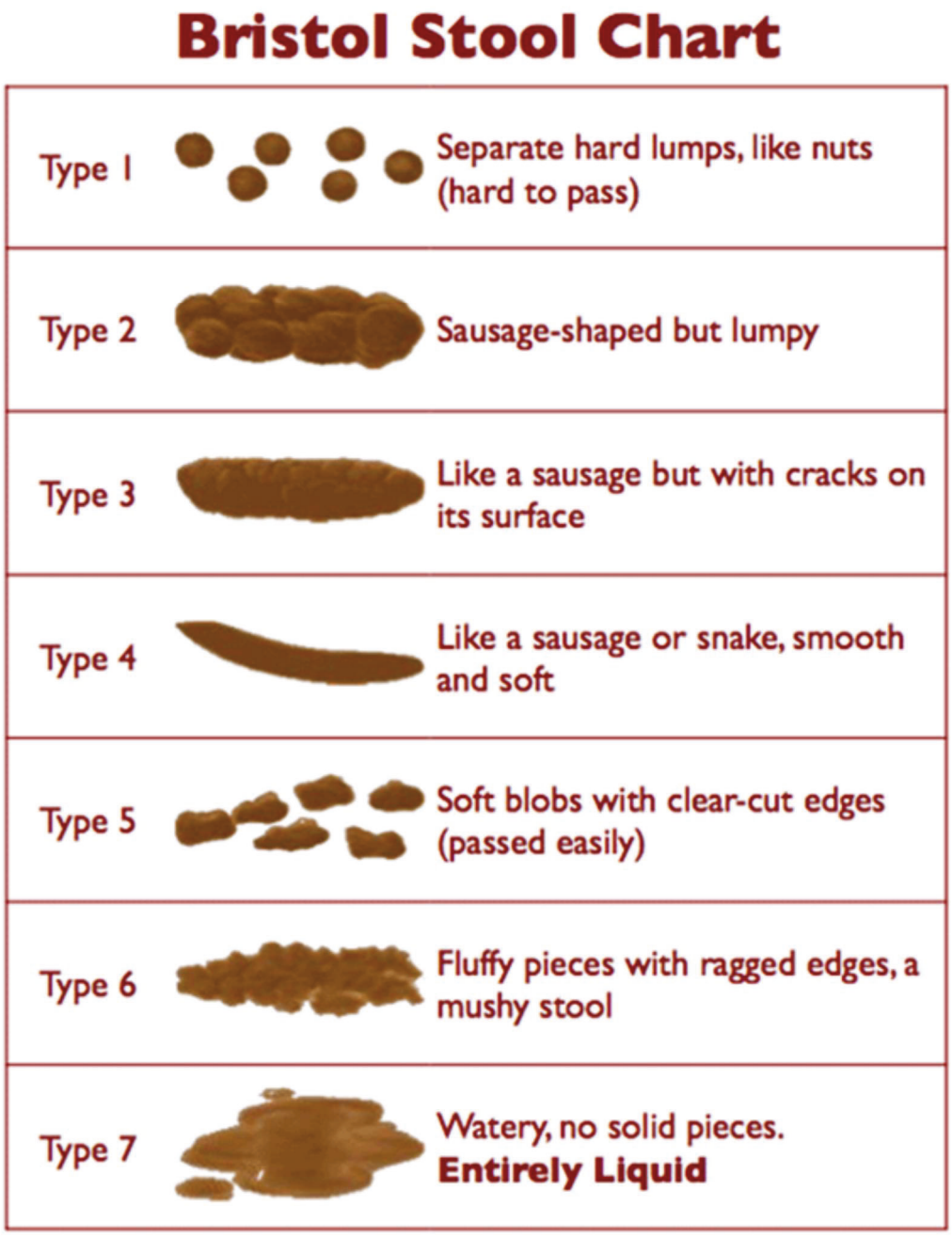
Loss of Response

The Investigator judges the subject to have responded to infliximab in the past and demonstrated a loss of response after a full and adequate course of infliximab based on the Investigator's assessment.

Intolerance to Infliximab

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

Appendix L. Bristol Stool Form Scale



Appendix M. SES-CD Scoring

SES-CD Scoring[8]

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (Ø 0.1 to 0.5 cm) 2 if large ulcers (Ø 0.5 to 2 cm) 3 if very large ulcers (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected Surface Enter: 0 if unaffected segments 1 if < 50% 2 if 50% – 75% 3 if > 75%						
Presence of Narrowing Enter: 0 if none 1 if single, can be passed 2 if multiple, can be passed 3 if cannot be passed						
					TOTAL =	

Appendix N. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

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

[redacted]
1 North Waukegan Road
North Chicago, IL 60064
United States

Has been changed to read:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064
United States

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-115
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 20 March 2017
Protocol Title: A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration	
Objectives: The objective of Study M14-115 is to evaluate efficacy and safety of higher induction and maintenance dosing regimens in subjects with moderately to severely active Crohn's disease.	
Investigators: Multicenter	
Study Sites: Approximately 150 sites worldwide.	
Study Population: Males and females ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active Crohn's disease, CDAI ≥ 220 and ≤ 450, and evidence of mucosal ulceration by Simple Endoscopic Score (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on screening endoscopy (or endoscopy performed within 45 days before Baseline), confirmed by a central reader.	
Number of Subjects to be Enrolled: Approximately 600 (360 in higher induction regimen group and 240 in standard induction regimen group) subjects with moderately to severely active Crohn's Disease, CDAI of ≥ 220 and ≤ 450 and evidence of mucosal ulceration, confirmed by centrally read endoscopy.	
Methodology: This Phase 3 study design includes the Screening Period followed by a 12-Week double-blind Induction Study and 44-Week double-blind Maintenance Study. The Induction Study will assess the efficacy and safety of two adalimumab induction regimens in achieving clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150 at Week 4, and endoscopic improvement, defined as Simplified Endoscopic Score for Crohn's Disease (SES-CD) ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12, in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration at Baseline. The Maintenance Study will assess the efficacy and safety of two adalimumab maintenance regimens in maintaining clinical and endoscopic improvements at Week 56. Analyses of the outcomes from the maintenance regimens are considered exploratory. During both the Induction Study and the Maintenance Study, visit week designations will represent weeks since first dose in the Induction Study. Week 0 (Baseline) will reflect the date of first adalimumab dosing in the Induction Study. Week 12 will represent the final assessment in the Induction Study. Week 56 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study).	

Methodology (Continued):

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 3:2 ratio at Baseline to receive a higher induction adalimumab regimen or standard induction adalimumab regimen during the double-blind Induction Study. Up to 25% of subjects with previous infliximab exposure may be enrolled. All subjects who complete the Induction Study (regardless of achievement of response at Week 12) will continue into the Maintenance Study. Assuming the Week 4 clinical remission rate will be approximately 50% for the higher induction dose regimen and approximately 30% for the standard dose regimen, a sample size of 600 (360 higher dose and 240 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts an expected ~50% increase in the proportion of subjects with endoscopic improvement compared to the standard adalimumab induction regimen. The observed rate of SES-CD ≤ 4 in Study M05-769 was 37% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for SES-CD ≤ 4 at Week 12 using the higher induction regimen is 55%. A sample size of 600 subjects (360 higher induction regimen and 240 standard induction regimen) will be adequate to detect at least an 18% treatment difference in endoscopic improvement rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 98% power at a 0.05 two-sided significance level.

Since clinical remission at the Week 4 endpoint and the endoscopic improvement at the Week 12 endpoint are not likely to be independent of each other, the power for the co-primary endpoints for the Induction Study is expected to be > 97% (see protocol for detailed assumptions of the sample size calculation).

The randomization of subjects for the Induction Study will be stratified by high-sensitivity C-Reactive Protein (hs-CRP) at Baseline (< 10 and ≥ 10 mg/L), using the Screening hs-CRP value, prior infliximab use, and Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline. Subjects with prior infliximab experience will be limited to 25% of the study population. Subjects assigned to the higher induction regimen will receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects will receive adalimumab 40 mg every other week (eow) through Week 12. Subjects assigned to the standard induction regimen will receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg at Week 2 and matching placebo at Week 3. At Week 4, subjects will receive adalimumab 40 mg every other week through Week 12.

Maintenance Study:

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of the two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen). The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and endoscopic response status (decrease in SES-CD > 50% from Baseline) per the site investigator reading at Week 12. Among Week 12 endoscopic responders, the randomization will be further stratified by endoscopic improvement, defined as achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Methodology (Continued):

Clinically Adjusted (CA) Regimen:

Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week (ew) as early as Week 14 if the subject's CDAI ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria below. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing.

Therapeutic Drug Monitoring (TDM) Regimen:

At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM will be determined by the dose adjustment criteria referenced in the table below. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.

The goal of the TDM regimen is to attain and maintain serum adalimumab levels above a reasonably high concentration levels in subjects for mucosal healing. Since exposure-endoscopic relationships are not currently available for adalimumab, clinical remission was used for selection of concentration threshold to be used in TDM arm. Based on the PK analyses of concentrations in Studies M02-403, M04-691 and M02-433, no concentration level could be identified as significant and reliable predictor of remission in adult CD. Therefore, the TDM regimen will be based on two concentration thresholds in conjunction with clinical response criteria as expected to occur in clinical setting. About 75% of the subjects who were in remission at Week 56 in Study M02-433 had serum concentration above 5 µg/mL. Therefore, the lower concentration threshold for the TDM regimen was selected as 5 µg/mL and any subject below 5 µg/mL concentration will be escalated to ew dosing. The second threshold was selected as 10 µg/mL, which is similar to the median concentrations (9.4 µg/mL at Week 56) observed in subjects who were in remission. The subjects with concentration above 5 and below 10 µg/mL may be dose escalated based on clinical response as outlined in the table below. The subjects with serum concentration above 10 µg/mL will not be dose escalated.

Methodology (Continued):

Adalimumab Dose Adjustment Criteria[a]

ADA Serum Concentration[b] (ug/mL)	CDAI[c]	hs-CRP[d] (mg/L)	Dose Change?
Clinically Adjusted Regimen			
any	< 220	< 10	no
any	any	≥ 10	yes; dose escalate to ew
any	≥ 220	any	yes; dose escalate to ew
Therapeutic Drug Monitoring Regimen			
< 5	any	any	yes; dose escalate to ew
5 – 10	< 220	< 10	no
5 – 10	any	≥ 10	yes; dose escalate to ew
5 – 10	≥ 220	any	yes; dose escalate to ew
> 10	any	any	no

a. For subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable, the investigator should contact the Study Designated Physician.

b. Measured from the serum concentration taken at the prior study visit.

c. Measured using hematocrit taken from prior study visit for CDAI calculation.

d. Measured using hs-CRP from the prior or current study visit.

The duration of the study could be up to 60 weeks which includes a Screening Period (1 – 4 weeks), a 12-week double-blind Induction Study and a 44-week Maintenance Study. The Screening Period may be extended as necessary after consultation with and approval by the AbbVie Study Designated Physician (SDP) for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results). There will also be a 70-day follow-up phone call for subjects who complete Week 56 or discontinue from the study prematurely.

Clinical evaluation will occur at Baseline, Weeks 2, 4, 6, 8, 12, 14, 20, 26, 28, 34, 40, 42, 48, and 56/Premature Discontinuation (PD) visits. An electronic diary will be dispensed at the Screening visit. In addition to routine physical examination, CDAI calculation, diary review, laboratory, adverse event, concomitant medication and vital sign assessments, the following will be collected:

- Results of study questionnaires (IBDQ, EQ-5D, WPAI) at Baseline, Week 4, Week 8, Week 12, Week 26, Week 40 and Week 56/PD.
- Calculation of the SFPS at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 14, Week 20, Week 26, Week 28, Week 34, Week 40, Week 42, Week 48 and Week 56/PD. The Screening visit results will serve as the Baseline value.
- Results of daily Bristol Stool Form Scale beginning at Baseline through Week 56/PD.
- Results of 11-point Abdominal Pain Rating Scale beginning at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.

Methodology (Continued):

- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.
- Serum biomarkers/mRNA at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Stool samples for analysis of fecal calprotectin during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Stool samples for microbiota metagenomic analyses during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Endoscopic evaluations, confirmed by central reader, will be done at Screening, Week 12, and Week 56/PD.
- An optional pharmacogenetic sample should be drawn at Baseline and Week 12.

Throughout the study, subjects will only be allowed to change the dosage of CD-specific concomitant medications as specified below:

- At Week 4, subjects who are taking corticosteroid therapy at Baseline will have their corticosteroid therapy tapered according to a tapering schedule specified in the clinical study protocol. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the Study Designated Physician (SDP) should be consulted for evaluation and approval.
- Subjects taking corticosteroids at Baseline who have a loss of satisfactory clinical response per the Investigator's judgment after the steroid taper has been initiated may have their corticosteroid dose increased per the Investigator's discretion during the study. Subjects in whom the maximum equivalent steroid dose exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have Baseline values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion

1. Males and females ≥ 18 and ≤ 75 years of age at Baseline.
2. Diagnosis of colonic, ileocolonic, or ileal Crohn's disease for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before Baseline, with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Simplified Endoscopic Score for Crohn's Disease (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on a screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader.

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

Main Inclusion (Continued)

4. Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450 at Baseline despite concurrent or prior treatment with a full and adequate course, in the opinion of the Investigator, of at least one of the following (oral corticosteroids and/or immunosuppressants or both as defined below):
   - Subject taking oral corticosteroids, excluding budesonide:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subjects with a dose > 10 and ≤ 40 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 and the duration of the current steroid course has been at least 14 days prior to Baseline.
   - Subject 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 and the duration of the current steroid course has been at least 14 days prior to Baseline;

   or,

   - At least a consecutive 42-day course of azathioprine, 6-MP or injectable MTX prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of at least 230 pmol/8 × 10^8 RBC to clarify a therapeutic level was achieved on the current dosing regimen 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.

     Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.

   or,

   - Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability, see Section 10.1.

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

Main Inclusion (Continued):

5. Subject may be included if they have previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD-related symptoms) or intolerance (in the opinion of the Investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. Subject has a negative TB Screening Assessment (including a PPD test or QuantiFERON TB Gold test [or equivalent]) and negative chest x-ray (CXR – PA and lateral view) at Screening. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.
7. 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 which result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
   - Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone releasing system (IUS)
   - Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
   - Vasectomized partner
   - Hormonal contraceptives for at least 90 days prior to study drug administration.

   Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol 0.5 mg are not considered adequate.
8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
9. Subject is judged to be in otherwise good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead electrocardiogram (ECG) performed during Screening.
10. 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 on azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who:
   - Has not been on these medications for at least 42 days prior to Baseline; or
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued these medications within 14 days of Baseline.

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

Main Exclusion (Continued):

3. Subject on oral aminosalicylates who:
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued use of aminosalicylates within 14 days of Baseline.
4. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide > 9 mg/day; or
   - Subject taking an oral corticosteroid (excluding budesonide):
     - dose > 10 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose > 10 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent, but has **not** been on a stable dose for at least 10 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline, or
   - Subject taking budesonide:
     - dose ≥ 6 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose ≥ 6 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose < 6 mg/day dose but has **not** been on a stable dose of at least 10 days prior to Baseline; or
     - dose < 6 mg/day but the current course has **not** been at least 14 days in duration prior to Baseline; or

   Has been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of inhalers.
5. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
6. Subject who has had surgical bowel resections within the past 6 months or is planning any resection at any time point while enrolled in the study.
7. Subject with a symptomatic bowel stricture.
8. Subject with an abdominal or peri-anal abscess.
9. Subject with an ostomy or ileoanal pouch.
10. Subject who has 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 (PML) including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab [Raptiva®]). Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).

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

Main Exclusion (Continued):

13. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.
14. Subject who previously received treatment with adalimumab or previously participated in an adalimumab clinical study.
15. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 60 days prior to Baseline.
16. Subject who previously received stem cell transplantation.
17. Subject who previously received fecal microbial transplantation.
18. Subject that received non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days prior to Screening and during the Screening Visit, except low-dose aspirin for prevention of heart attacks, unstable angina or transient ischemic attacks or topical NSAIDs.
19. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives for non-Crohn's disease related infections within 14 days prior to the Baseline Visit.
20. Subjects on Crohn's disease related antibiotics that have not been on stable doses for at least 28 days prior to Baseline. Subjects on Crohn's disease related antibiotics that have discontinued these medications within 28 days of Baseline are excluded.
21. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.
22. Subject with positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening period.
23. Screening laboratory and other analyses show any of the following abnormal results:
    - AST, ALT > 1.75 × 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.
24. Known hypersensitivity to adalimumab or its excipients.
25. Subject who has previously used infliximab:
    - and had not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction;

      or
    - who used infliximab within 56 days of Baseline.
26. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
27. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).
28. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

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

Main Exclusion (Continued):

29. Subjects with a positive result for the Hepatitis B surface antigen (HBs Ag) will be excluded. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

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

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

        * For HBs Ab test results, a (–) result is equivalent to nonreactive and a (+) result is equivalent to reactive.

30. Chronic recurring infections.
31. Subject with active TB.
32. Subject with latent TB infection unless there is evidence the subject initiated and completed a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.
33. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study.
34. Subject with a previous history of dysplasia of the gastrointestinal tract, or found to have dysplasia in any biopsy performed during the Screening endoscopy or endoscopy performed within 45 days before Baseline.
35. Positive pregnancy test at Screening (serum) or Baseline (urine).
36. Female subjects who are breastfeeding or considering becoming pregnant during the study.
37. History of clinically significant drug or alcohol abuse in the last 12 months.
38. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
39. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
40. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Products:	Adalimumab (40 mg/0.8 mL)
Double-Blind Induction	Subjects will be randomized to receive one of 2 double-blind adalimumab Induction Study regimens.
Doses:	**(Higher Induction Regimen)** 160 mg at Baseline, Weeks 1, 2, and 3, and 40 mg at Week 4, continuing at 40 mg every other week through Week 12. **(Standard Induction Regimen)** 160 mg at Baseline and matching placebo at Week 1, 80 mg at Week 2 and matching placebo at Week 3 and 40 mg every other week beginning at Week 4 through Week 12.
Double-Blind Maintenance	Subjects will receive one of two double-blind adalimumab Maintenance Study regimens.
Doses: NOTE: In order to retain blinding across regimens, all subjects who do not meet the criteria for dose escalation in either maintenance regimen will receive matching placebo injections in addition to the adalimumab injection.	Clinically Adjusted (CA) Regimen: Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week starting at Week 14 if CDAI is ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria table. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing. Therapeutic Drug Monitoring (TDM) Regimen: At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM regimen will be determined by the dose adjustment criteria table. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment:

The study will include a Screening Period of 1 – 4 weeks, a double-blind Induction Study of 12 weeks, and a double-blind Maintenance Study of 44 weeks. There will also be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely.

Criteria for Evaluation:

Efficacy Endpoints:

Subjects participating in the Induction Study randomized to the higher adalimumab induction dose regimen will be compared to those subjects randomized to the standard adalimumab induction regimen. Subject data from the Maintenance Study will be used for exploratory analyses.

Co-Primary Induction Study Efficacy Endpoints:

- Proportion of subjects who achieve a CDAI < 150 at Week 4.
- Proportion of subjects who achieve an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12.

Ranked Secondary Endpoints:

1. Proportion of subjects with sustained clinical remission (CDAI < 150) at both Weeks 4 and 12.
2. Proportion of subjects with CDAI < 150 at Week 4 and SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12.
3. Proportion of subjects with clinical remission (CDAI < 150) at Week 12.
4. Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 12 among subjects taking corticosteroids at Baseline.
5. Proportion of subjects with endoscopic response (decrease > 50% SES-CD from baseline) at Week 12.
6. Change from Baseline in fecal calprotectin level at Week 4.
7. Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 μg/g at Week 4.
8. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g at Week 4.
9. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore > 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 12.
10. Proportion of subjects who achieve an SES-CD ≤ 2 at Week 12.
11. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 4.
12. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 12.
13. Change in IBDQ from baseline at Week 4.
14. Change in IBDQ from baseline at Week 12.

Endpoints for Exploratory Maintenance Study:

- Proportion of subjects who achieve endoscopic improvement (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic improvement at Week 12.
- Proportion of subjects who achieve a CDAI < 150 at Week 56 among subjects who achieve CDAI < 150 at Week 12.

All other efficacy and exploratory endpoints will be non-ranked.

Additional analyses are outlined in the protocol.

Criteria for Evaluation (Continued):

Pharmacokinetic:

Blood samples will be collected for measurement of serum adalimumab concentration just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/Premature Discontinuation and anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56PD.

Blood samples will also be collected for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.

Exploratory Research Using Intestinal Mucosal Biopsy Samples (Optional):

Optional intestinal biopsies will be collected with consent at Screening, Week 12, and Week 56 or at premature discontinuation. The purpose of these samples is to test potential biomarker signatures and new drug targets for IBD. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

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 co-primary efficacy variables for the Induction Study are proportion of subjects with moderately to severely active CD that have achieved clinical remission, defined as CDAI < 150, at Week 4 and proportion of subjects with moderately to severely active CD that have achieved endoscopic improvement defined as an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12. The comparison between treatment groups for the two co-primary efficacy variables will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by hs-CRP at Baseline (< 10 and ≥ 10 mg/L) (the Screening hs-CRP will serve as the Baseline value), prior infliximab use, and Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline. 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 or missing SES-CD at Week 12 will be imputed using the non-responder imputation (NRI) approach. For Week 4 clinical remission, LOCF, OC and multiple imputation methods will be used as sensitivity analyses. For Week 12 endoscopic improvement, LOCF and OC will be used as sensitivity analyses.

Secondary efficacy variables for the Induction Study are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at 0.050 (2-sided) in ranked endpoint order until the significance level exceeds 0.05. No additional statistically significant treatment differences may be declared after the first ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables.

Statistical Methods (Continued):

Efficacy (Continued):

In general, continuous secondary efficacy variables, including all efficacy variables for Maintenance Study, 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 data. NRI for missing data will be used for categorical endpoints. Both last observation carried forward (LOCF) and observed case (OC) analyses will be performed for continuous endpoint. The LOCF analysis is considered primary for inferential purposes. In addition, Mixed-Effect Model Repeated Measure (MMRM) will be applied, wherever appropriate, as a sensitivity analysis for the longitudinal continuous endpoints.

Pharmacokinetic:

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

Immunogenicity:

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

Safety:

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety set.
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 for subjects who do not participate in the OLE or until first dose of study drug in the OLE study if the subject is a study completer and is enrolled in the OLE. Treatment-emergent AEs will be summarized separately for: a) Baseline to Week 12; b) Week 12 to Week 56; c) Baseline to Week 56 (overall study duration). An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 15.1 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 group differences in the overall incidence of treatment-emergent AEs will be assessed with Fisher's exact test for each preferred term.

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.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M14-115
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 27 November 2018
Protocol Title: A Multicenter, Randomized, Double-Blind Study to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration	
Objectives: The objective of Study M14-115 is to evaluate efficacy and safety of higher induction and maintenance dosing regimens in subjects with moderately to severely active Crohn's disease.	
Investigators: Multicenter	
Study Sites: Approximately 150 sites worldwide.	
Study Population: Males and females ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active Crohn's disease, CDAI ≥ 220 and ≤ 450, and evidence of mucosal ulceration by Simple Endoscopic Score (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on screening endoscopy (or endoscopy performed within 45 days before Baseline), confirmed by a central reader.	
Number of Subjects to be Enrolled: Approximately 500 (300 in higher induction regimen group and 200 in standard induction regimen group) subjects with moderately to severely active Crohn's Disease, CDAI of ≥ 220 and ≤ 450 and evidence of mucosal ulceration, confirmed by centrally read endoscopy.	
Methodology: This Phase 3 study design includes the Screening Period followed by a 12-Week double-blind Induction Study and 44-Week double-blind Maintenance Study. The Induction Study will assess the efficacy and safety of two adalimumab induction regimens in achieving clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150 at Week 4, and endoscopic response, defined as a decrease in Simplified Endoscopic Score for Crohn's Disease (SES-CD) > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), as scored by central reviewer, at Week 12; in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration at Baseline. The Maintenance Study will assess the efficacy and safety of two adalimumab maintenance regimens in maintaining clinical and endoscopic improvements at Week 56. Analyses of the outcomes from the maintenance regimens are considered exploratory. During both the Induction Study and the Maintenance Study, visit week designations will represent weeks since first dose in the Induction Study. Week 0 (Baseline) will reflect the date of first adalimumab dosing in the Induction Study. Week 12 will represent the final assessment in the Induction Study. Week 56 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study).	

Methodology (Continued):

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 3:2 ratio at Baseline to receive a higher induction adalimumab regimen or standard induction adalimumab regimen during the double-blind Induction Study. Up to 25% of subjects with previous infliximab exposure may be enrolled. All subjects who complete the Induction Study (regardless of achievement of response at Week 12) will continue into the Maintenance Study. Assuming the Week 4 clinical remission rate will be approximately 50% for the higher induction dose regimen and approximately 30% for the standard dose regimen, a sample size of 500 (300 higher dose and 200 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts an expected ~50% increase in the proportion of subjects with endoscopic response compared to the standard adalimumab induction regimen. The observed rate of endoscopic response in Study M05-769 was 44% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for endoscopic response at Week 12 using the higher induction regimen is 66%. A sample size of 500 subjects (300 higher induction regimen and 200 standard induction regimen) will be adequate to detect at least a 22% treatment difference in endoscopic response rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 99% power at a 0.05 two-sided significance level.

Since clinical remission at the Week 4 endpoint and the endoscopic response at the Week 12 endpoint are not likely to be independent of each other, the power for the co-primary endpoints for the Induction Study is expected to be > 98% (see protocol for detailed assumptions of the sample size calculation).

The randomization of subjects for the Induction Study will be stratified by high-sensitivity C-Reactive Protein (hs-CRP) at Baseline (< 10 and ≥ 10 mg/L), using the Screening hs-CRP value, prior infliximab use, and Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline. Subjects with prior infliximab experience will be limited to 25% of the study population. Subjects assigned to the higher induction regimen will receive blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects will receive adalimumab 40 mg every other week (eow) through Week 12. Subjects assigned to the standard induction regimen will receive blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg at Week 2 and matching placebo at Week 3. At Week 4, subjects will receive adalimumab 40 mg every other week through Week 12.

Maintenance Study:

At Week 12, subjects will be re-randomized in a 1:1 ratio to one of the two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen). The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Methodology (Continued):

Clinically Adjusted (CA) Regimen:

Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week (ew) as early as Week 14 if the subject's CDAI ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria below. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing.

Therapeutic Drug Monitoring (TDM) Regimen:

At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM will be determined by the dose adjustment criteria referenced in the table below. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.

The goal of the TDM regimen is to attain and maintain serum adalimumab levels above a reasonably high concentration levels in subjects for mucosal healing. Since exposure-endoscopic relationships are not currently available for adalimumab, clinical remission was used for selection of concentration threshold to be used in TDM arm. Based on the PK analyses of concentrations in Studies M02-403, M04-691 and M02-433, no concentration level could be identified as significant and reliable predictor of remission in adult CD. Therefore, the TDM regimen will be based on two concentration thresholds in conjunction with clinical response criteria as expected to occur in clinical setting. About 75% of the subjects who were in remission at Week 56 in Study M02-433 had serum concentration above 5 µg/mL. Therefore, the lower concentration threshold for the TDM regimen was selected as 5 µg/mL and any subject below 5 µg/mL concentration will be escalated to ew dosing. The second threshold was selected as 10 µg/mL, which is similar to the median concentrations (9.4 µg/mL at Week 56) observed in subjects who were in remission. The subjects with concentration above 5 and below 10 µg/mL may be dose escalated based on clinical response as outlined in the table below. The subjects with serum concentration above 10 µg/mL will not be dose escalated.

Methodology (Continued):

Adalimumab Dose Adjustment Criteria[a]

ADA Serum Concentration[b] (ug/mL)	CDAI[c]	hs-CRP[d] (mg/L)	Dose Change?
Clinically Adjusted Regimen			
any	< 220	< 10	no
any	any	≥ 10	yes; dose escalate to ew
any	≥ 220	any	yes; dose escalate to ew
Therapeutic Drug Monitoring Regimen			
< 5	any	any	yes; dose escalate to ew
5 – 10	< 220	< 10	no
5 – 10	any	≥ 10	yes; dose escalate to ew
5 – 10	≥ 220	any	yes; dose escalate to ew
> 10	any	any	no

a. For subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable, the investigator should contact the Study Designated Physician.

b. Measured from the serum concentration taken at the prior study visit.

c. Measured using hematocrit taken from prior study visit for CDAI calculation.

d. Measured using hs-CRP from the prior or current study visit.

The duration of the study could be up to 60 weeks which includes a Screening Period (1 – 4 weeks), a 12-week double-blind Induction Study and a 44-week Maintenance Study. The Screening Period may be extended as necessary after consultation with and approval by the AbbVie Study Designated Physician (SDP) for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results). There will also be a 70-day follow-up phone call for subjects who complete Week 56 or discontinue from the study prematurely.

Clinical evaluation will occur at Baseline, Weeks 2, 4, 6, 8, 12, 14, 20, 26, 28, 34, 40, 42, 48, and 56/Premature Discontinuation (PD) visits. An electronic diary will be dispensed at the Screening visit. In addition to routine physical examination, CDAI calculation, diary review, laboratory, adverse event, concomitant medication and vital sign assessments, the following will be collected:

- Results of study questionnaires (IBDQ, EQ-5D, WPAI) at Baseline, Week 4, Week 8, Week 12, Week 26, Week 40 and Week 56/PD.
- Calculation of the SFPS at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 14, Week 20, Week 26, Week 28, Week 34, Week 40, Week 42, Week 48 and Week 56/PD. The Screening visit results will serve as the Baseline value.
- Results of daily Bristol Stool Form Scale beginning at Baseline through Week 56/PD.
- Results of 11-point Abdominal Pain Rating Scale beginning at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of adalimumab concentrations just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.

Methodology (Continued):

- Serum for measurement of Anti-Adalimumab Antibodies (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56/PD.
- Serum for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.
- Serum biomarkers/mRNA at Baseline, Week 2, Week 4, Week 8, Week 12, Week 26, Week 40, and Week 56/PD.
- Stool samples for analysis of fecal calprotectin during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Stool samples for microbiota metagenomic analyses during Screening, at Week 4, Week 12, Week 26, and Week 56/PD.
- Endoscopic evaluations, confirmed by central reader, will be done at Screening, Week 12, and Week 56/PD.
- An optional pharmacogenetic sample should be drawn at Baseline and Week 12.

Throughout the study, subjects will only be allowed to change the dosage of CD-specific concomitant medications as specified below:

- At Week 4, subjects who are taking corticosteroid therapy at Baseline will have their corticosteroid therapy tapered according to a tapering schedule specified in the clinical study protocol. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, the Study Designated Physician (SDP) should be consulted for evaluation and approval.
- Subjects taking corticosteroids at Baseline who have a loss of satisfactory clinical response per the Investigator's judgment after the steroid taper has been initiated may have their corticosteroid dose increased per the Investigator's discretion during the study. Subjects in whom the maximum equivalent steroid dose exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.
- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion

1. Males and females ≥ 18 and ≤ 75 years of age at Baseline.
2. Diagnosis of colonic, ileocolonic, or ileal Crohn's disease for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before Baseline, with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Simplified Endoscopic Score for Crohn's Disease (SES-CD) ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on a screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader.

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

Main Inclusion (Continued)

4. Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450 at Baseline despite concurrent or prior treatment with a full and adequate course, in the opinion of the Investigator, of at least one of the following (oral corticosteroids and/or immunosuppressants or both as defined below):
   - Subject taking oral corticosteroids, excluding budesonide:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subjects with a dose > 10 and ≤ 40 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 and the duration of the current steroid course has been at least 14 days prior to Baseline.
   - Subject 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 and the duration of the current steroid course has been at least 14 days prior to Baseline;

   or,

   - At least a consecutive 42-day course of azathioprine, 6-MP or injectable MTX prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-TGN level of at least 230 pmol/8 × 10^8 RBC to clarify a therapeutic level was achieved on the current dosing regimen 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.

     Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.

   or,

   - Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability, see Section 10.1.

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

Main Inclusion (Continued):

5. Subject may be included if they have previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD-related symptoms) or intolerance (in the opinion of the Investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. Subject has a negative TB Screening Assessment (including a PPD test or QuantiFERON TB Gold test [or equivalent]) and negative chest x-ray (CXR – PA and lateral view) at Screening. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.
7. 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 which result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
   - Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone releasing system (IUS)
   - Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
   - Vasectomized partner
   - Hormonal contraceptives for at least 90 days prior to study drug administration.

   Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol 0.5 mg are not considered adequate.
8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
9. Subject is judged to be in otherwise good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead electrocardiogram (ECG) performed during Screening.
10. 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 on azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who:
   - Has not been on these medications for at least 42 days prior to Baseline; or
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued these medications within 14 days of Baseline.

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

Main Exclusion (Continued):

3. Subject on oral aminosalicylates who:
   - Has not been on stable doses of these medications for at least 28 days prior to Baseline; or
   - Has discontinued use of aminosalicylates within 14 days of Baseline.
4. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide > 9 mg/day; or
   - Subject taking an oral corticosteroid (excluding budesonide):
     - dose > 10 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose > 10 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent, but has **not** been on a stable dose for at least 10 days prior to Baseline; or
     - dose ≤ 10 mg/day or equivalent but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline, or
   - Subject taking budesonide:
     - dose ≥ 6 mg/day, but has **not** been on a stable dose for at least 7 days prior to Baseline; or
     - dose ≥ 6 mg/day, but has **not** been on a current steroid course for at least 14 days prior to Baseline; or
     - dose < 6 mg/day dose but has **not** been on a stable dose of at least 10 days prior to Baseline; or
     - dose < 6 mg/day but the current course has **not** been at least 14 days in duration prior to Baseline; or

   Has been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of inhalers.
5. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
6. Subject who has had surgical bowel resections within the past 6 months or is planning any resection at any time point while enrolled in the study.
7. Subject with a symptomatic bowel stricture.
8. Subject with an abdominal or peri-anal abscess.
9. Subject with an ostomy or ileoanal pouch.
10. Subject who has 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 (PML) including participation in a clinical trial of investigational agents targeting white cell trafficking (e.g., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab [Raptiva®]). Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).

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

Main Exclusion (Continued):

13. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.
14. Subject who previously received treatment with adalimumab or previously participated in an adalimumab clinical study.
15. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 60 days prior to Baseline.
16. Subject who previously received stem cell transplantation.
17. Subject who previously received fecal microbial transplantation.
18. Subject that received non-steroidal anti-inflammatory drugs (NSAIDs) within 14 days prior to Screening and during the Screening Visit, except low-dose aspirin for prevention of heart attacks, unstable angina or transient ischemic attacks or topical NSAIDs.
19. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives for non-Crohn's disease related infections within 14 days prior to the Baseline Visit.
20. Subjects on Crohn's disease related antibiotics that have not been on stable doses for at least 28 days prior to Baseline. Subjects on Crohn's disease related antibiotics that have discontinued these medications within 28 days of Baseline are excluded.
21. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.
22. Subject with positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening period.
23. Screening laboratory and other analyses show any of the following abnormal results:
    - AST, ALT > 1.75 × 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.
24. Known hypersensitivity to adalimumab or its excipients.
25. Subject who has previously used infliximab:
    - and had not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction;

      or
    - who used infliximab within 56 days of Baseline.
26. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
27. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).
28. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

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

Main Exclusion (Continued):

29. Subjects with a positive result for the Hepatitis B surface antigen (HBs Ag) will be excluded. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

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

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

        * For HBs Ab test results, a (–) result is equivalent to nonreactive and a (+) result is equivalent to reactive.

30. Chronic recurring infections.
31. Subject with active TB.
32. Subject with latent TB infection unless there is evidence the subject initiated and completed a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, prior to Baseline.
33. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study.
34. Subject with a previous history of dysplasia of the gastrointestinal tract, or found to have dysplasia in any biopsy performed during the Screening endoscopy or endoscopy performed within 45 days before Baseline.
35. Positive pregnancy test at Screening (serum) or Baseline (urine).
36. Female subjects who are breastfeeding or considering becoming pregnant during the study.
37. History of clinically significant drug or alcohol abuse in the last 12 months.
38. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
39. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
40. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Investigational Products:	Adalimumab (40 mg/0.8 mL)
Double-Blind Induction	Subjects will be randomized to receive one of 2 double-blind adalimumab Induction Study regimens.
Doses:	**(Higher Induction Regimen)** 160 mg at Baseline, Weeks 1, 2, and 3, and 40 mg at Week 4, continuing at 40 mg every other week through Week 12. **(Standard Induction Regimen)** 160 mg at Baseline and matching placebo at Week 1, 80 mg at Week 2 and matching placebo at Week 3 and 40 mg every other week beginning at Week 4 through Week 12.
Double-Blind Maintenance	Subjects will receive one of two double-blind adalimumab Maintenance Study regimens.
Doses: NOTE: In order to retain blinding across regimens, all subjects who do not meet the criteria for dose escalation in either maintenance regimen will receive matching placebo injections in addition to the adalimumab injection.	Clinically Adjusted (CA) Regimen: Subjects randomized to the clinically adjusted regimen will receive 40 mg adalimumab every other week beginning at Week 12. The adalimumab dose will be escalated to every week starting at Week 14 if CDAI is ≥ 220 or hs-CRP ≥ 10 mg/L (using results from the prior or current visit) as shown by the dose adjustment criteria table. These subjects will also be allowed to escalate at unscheduled visits that may occur only on Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the clinically adjusted regimen are escalated, they will remain on 40 mg ew dosing. Therapeutic Drug Monitoring (TDM) Regimen: At Weeks 14, 28 and 42, the adalimumab dose for subjects randomized to the TDM regimen will be determined by the dose adjustment criteria table. Doses will be determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who meet criteria for dose escalation at Weeks 14, 28 or 42, subjects will receive 40 mg weekly.
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment:

The study will include a Screening Period of 1 – 4 weeks, a double-blind Induction Study of 12 weeks, and a double-blind Maintenance Study of 44 weeks. There will also be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely.

Criteria for Evaluation:

Efficacy Endpoints:

Subjects participating in the Induction Study randomized to the higher adalimumab induction dose regimen will be compared to those subjects randomized to the standard adalimumab induction regimen. Subject data from the Maintenance Study will be used for exploratory analyses.

Induction Study Co-Primary Efficacy Endpoints:

- Proportion of subjects who achieve a CDAI < 150 at Week 4.
- Proportion of subjects with decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.

Induction Study Ranked Secondary Endpoints:

1. Proportion of subjects with sustained clinical remission (CDAI < 150) at both Weeks 4 and 12.
2. Proportion of subjects with CDAI < 150 at Week 4 and decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.
3. Proportion of subjects with clinical remission (CDAI < 150) at Week 12.
4. Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 12 among subjects taking corticosteroids at Baseline.
5. Proportion of subjects with endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 12.
6. Change from Baseline in fecal calprotectin level at Week 4.
7. Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 μg/g at Week 4.
8. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g at Week 4.
9. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore > 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 12.
10. Proportion of subjects who achieve an SES-CD ≤ 2 at Week 12.
11. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 4.
12. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 12.
13. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 4.
14. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 12.
15. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 12.

All other efficacy and exploratory endpoints will be non-ranked.

Criteria for Evaluation (Continued):

All endpoints for the Exploratory Maintenance Study will be non-ranked.

Pharmacokinetic:

Blood samples will be collected for measurement of serum adalimumab concentration just prior to dosing at Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 26, Week 40, and Week 56/Premature Discontinuation and anti-adalimumab antibody (AAA) just prior to dosing at Baseline, Week 4, Week 12, Week 26, Week 40, and Week 56PD.

Blood samples will also be collected for measurement of infliximab serum levels and Human Anti-Chimeric Antibodies (HACA) just prior to dosing at Baseline.

Exploratory Research Using Intestinal Mucosal Biopsy Samples (Optional):

Optional intestinal biopsies will be collected with consent at Screening, Week 12, and Week 56 or at premature discontinuation. The purpose of these samples is to test potential biomarker signatures and new drug targets for IBD. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

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 co-primary efficacy variables for the Induction Study are proportion of subjects with moderately to severely active CD that have achieved clinical remission, defined as CDAI < 150, at Week 4 and proportion of subjects with moderately to severely active CD that have achieved a decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline), at Week 12. The comparison between treatment groups for the two co-primary efficacy variables will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by hs-CRP at Baseline (< 10 and ≥ 10 mg/L) (the Screening hs-CRP will serve as the Baseline value), prior infliximab use, and Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline. 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. For the evaluation of co-primary endpoints, missing data of CDAI at Week 4 or missing SES-CD at Week 12 will be imputed using the non-responder imputation (NRI) approach. For Week 4 clinical remission, LOCF, OC and multiple imputation methods will be used as sensitivity analyses. For Week 12 endoscopic response (decrease in SES-CD > 50% from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]), OC will be used as sensitivity analysis.

Statistical Methods (Continued):

Efficacy (Continued):

Secondary efficacy variables for the Induction Study are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at significance level of 0.050 (2-sided) in ranked endpoint order until the significance level exceeds 0.05. No additional statistically significant treatment differences may be declared after the first ranked endpoint fails to achieve statistical significance at a two-sided significance level of 0.05. The second group includes all other secondary variables.

In general, continuous secondary efficacy variables, including all efficacy variables for Maintenance Study, 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 is used for categorical endpoints. NRI for missing data will be used for categorical endpoints. Both last observation carried forward (LOCF) and observed case (OC) analyses will be performed for continuous endpoints. The LOCF analysis is considered primary for inferential purposes. In addition, Mixed-Effect Model Repeated Measure (MMRM) will be applied, wherever appropriate, as a sensitivity analysis for the longitudinal continuous endpoints.

Pharmacokinetic:

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

Immunogenicity:

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

Safety:

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

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 for subjects who do not participate in the OLE or until first dose of study drug in the OLE study if the subject is a study completer and is enrolled in the OLE. Treatment-emergent AEs will be summarized separately for: a) Baseline to Week 12; b) Week 12 to Week 56; c) Baseline to Week 56 (overall study duration). An overview of treatment-emergent AEs, including AEs of special interest, adverse events leading to death and adverse events leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 20.1 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.

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.

Section 4.0 Study Objective
First paragraph previously said:

The primary objective of this study is to assess the efficacy and safety of two adalimumab induction regimens in achieving clinical remission (CDAI < 150) at Week 4 and endoscopic improvement defined as Simplified Endoscopic Score for Crohn's Disease (SES-CD) ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12 in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration at Baseline.

Has been changed to read:

The primary objective of this study is to assess the efficacy and safety of two adalimumab induction regimens in achieving clinical remission (CDAI < 150) at Week 4 and endoscopic response defined as decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12, in subjects with moderately to severely active Crohn's disease and evidence of mucosal ulceration at Baseline.

Section 5.1 Overall Study Design and Plan: Description
First paragraph, second sentence previously read:

No placebo arm is planned since there is well-documented efficacy of adalimumab in CD and because the purpose of this study is to achieve better efficacy than the standard induction and maintenance regimens in terms of clinical remission and endoscopic improvement.

Has been changed to read:

No placebo arm is planned since there is well-documented efficacy of adalimumab in CD and because the purpose of this study is to achieve better efficacy than the standard induction and maintenance regimens in terms of clinical remission and endoscopic response.

Section 5.1 Overall Study Design and Plan: Description
Second paragraph previously read:

Approximately 600 adult subjects with active Crohn's disease, defined as having a CDAI of ≥ 220 and ≤ 450 and evidence of mucosal ulceration defined as SES-CD ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a centrally read endoscopy, will be enrolled at approximately 150 sites worldwide.

Has been changed to read:

Approximately 500 adult subjects with active Crohn's disease, defined as having a CDAI of ≥ 220 and ≤ 450 and evidence of mucosal ulceration defined as SES-CD ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a centrally read endoscopy, will be enrolled at approximately 150 sites worldwide.

Section 5.1 Overall Study Design and Plan: Description
Third paragraph, last sentence previously read:

Assuming the Week 4 clinical remission rate will be approximately 50% for the higher induction dose regimen and approximately 30% for the standard dose regimen, a sample size of 600 (360 higher dose and 240 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Has been changed to read:

Assuming the Week 4 clinical remission rate will be approximately 50% for the higher induction dose regimen and approximately 30% for the standard dose regimen, a sample size of 500 (300 higher dose and 200 standard dose) will be adequate to detect at least a

20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph previously read:

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts an expected ~50% increase in the proportion of subjects with endoscopic improvement compared to the standard adalimumab induction regimen. The observed rate of SES-CD ≤ 4 in Study M05-769 was 37% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for SES-CD ≤ 4 using the higher induction regimen is 55%. A sample size of 600 subjects (360 higher induction regimen and 240 standard induction regimen) will be adequate to detect at least a 18% treatment difference in endoscopic improvement rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 98% power at a 0.05 two-sided significance level.

Has been changed to read:

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts an expected ~50% increase in the proportion of subjects with endoscopic response compared to the standard adalimumab induction regimen. The observed rate of endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) in Study M05-769 was 44% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for endoscopic response at Week 12 using the higher induction regimen is 66%. A sample size of 500 subjects (300 higher induction regimen and 200 standard induction regimen) will be adequate to detect at least a 22% treatment difference in endoscopic response (decrease >50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 99% power at a 0.05 two-sided significance level.

Section 5.1 Overall Study Design and Plan: Description
Fifth paragraph previously read:

Since the clinical remission at Week 4 endpoint and the endoscopic improvement at Week 12 endpoint are likely not independent of each other, the power for the co-primary endpoints for the study is expected to be > 97% (see Section 8.2 for detailed assumptions of the sample size calculation).

Has been changed to read:

Since the clinical remission at Week 4 endpoint and the endoscopic response at Week 12 endpoint are likely not independent of each other, the power for the co-primary endpoints for the study is expected to be > 98% (see Section 8.2 for detailed assumptions of the sample size calculation).

Section 5.1 Overall Study Design and Plan: Description
Eighth paragraph, second and third sentence previously read:

The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and endoscopic response status (decrease in SES-CD > 50% from Baseline) per the site investigator reading at Week 12. Among Week 12 endoscopic responders, the randomization will be further stratified by endoscopic improvement, defined as achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus Baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Has been changed to read:

The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus Baseline and no

subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Section 5.1 Overall Study Design and Plan: Description
Fourteenth paragraph, second bullet
Second sentence previously read:

Subjects in whom the maximum steroid dose equivalent exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., will be considered non-responders for categorical endpoints and will have Baseline values carried forward for non-categorical assessments) from that point forward.

Has been changed to read:

Subjects in whom the maximum steroid dose equivalent exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward.

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

The study was designed to enroll 600 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study was designed to enroll 500 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.2.3.2 Concomitant Therapy
Sixth paragraph, second sentence previously read:

Subjects in whom the maximum equivalent steroid dose exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., they will be considered non-responders for

categorical endpoints and will have Baseline values carried forward for non-categorical assessments) from that point forward.

Has been changed to read:

Subjects in whom the maximum equivalent steroid dose exceeds the dose used at Baseline will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward.

Section 5.2.3.2 Concomitant Therapy
Sixth paragraph
Add: new last sentence

In addition, subjects in whom the CD-related corticosteroids that were not being taken at Baseline and are initiated during the study will be censored for efficacy assessments (i.e., they will be considered non-responders for categorical endpoints and will have the last non-missing values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.

Section 5.2.3.2 Concomitant Therapy
Ninth paragraph previously read:

Subjects in whom the following CD-related medications (oral or rectal aminosalicylates, systemic or rectal corticosteroids thiopurines and MTX) that were not being taken at Baseline and are initiated during the study or who have dosages of these medications increased to greater than the dose taken at Baseline will be censored for efficacy assessments (i.e., will be considered non-responders for categorical endpoints and will have Baseline values carried forward for non-categorical assessments) from that point forward. These subjects will continue to be evaluated in the safety population.

Has been changed to read:

Subjects in whom the following CD-related medications (oral or rectal aminosalicylates, thiopurines and MTX) that were not being taken at Baseline and are initiated during the

study or who have dosages of these medications increased to greater than the dose taken at Baseline is prohibited during the study, except in the event of moderate-to-severe treatment related toxicities and after discussion with the AbbVie TA MD.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Collection of Samples for Infliximab and HACA Assays
Last paragraph previously read:

The total number of samples planned will not exceed 600 (2 samples × 300 subjects) for the entire study.

Has been changed to read:

The total number of samples planned will not exceed 500 (2 samples × 300 subjects) for the entire study.

Section 5.3.3.1 Co-Primary Variables for Induction Study
Second bullet previously read:

Proportion of subjects who achieve SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12.

Has been changed to read:

Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 12.

Section 5.3.3.2 Secondary Variables for Induction Study
Item 2, 5, 13, and 14 previously read:

2. Proportion of subjects with CDAI < 150 at Week 4 and SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12.
5. Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Baseline) at Week 12.

13. Change in IBDQ from Baseline at Week 4.
14. Change in IBDQ from Baseline at Week 12.

Has been changed to read:

2. Proportion of subjects with CDAI < 150 at Week 4 and endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 12.
5. Proportion of subjects with endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 12.
13. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 4.
14. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 12.
15. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 12.

Section 5.3.3.2 Secondary Variables for Induction Study
Tenth bullet previously read:

Change in IBDQ from Baseline at Week 8.

Has been changed to read:

Change in IBDQ total score and individual IBDQ domain scores (bowel, emotional, social, systemic) from Baseline at each scheduled visit in Induction Study.

Section 5.3.3.2 Secondary Variables for Induction Study
Add: new thirteenth bullet

Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 4.

Section 5.3.3.2 Secondary Variables for Induction Study
Eighteenth bullet previously read:

- Change in Bristol Stool Scale score from Baseline at each scheduled visit in Induction Study.

Has been changed to read:

- Change in Bristol Stool Chart score from Baseline at each scheduled visit in Induction Study.
- Proportion of subjects who achieve Bristol Stool Chart response at each scheduled visit in Induction Study.

Section 5.3.3.2 Secondary Variables for Induction Study
Thirtieth and Thirty-first bullet previously read:

- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 1.5 (and not worse than baseline) and average daily abdominal pain ≤ 1.0 (and not worse than baseline), at each scheduled visit in Induction Study.
- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline or average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline, at each scheduled visit in Induction Study.

Has been changed to read:

- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than baseline) and average daily

abdominal pain ≤ 1.0 (and not worse than baseline), at each scheduled visit in Induction Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.

- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline or average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline, at each scheduled visit in Induction Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
First bullet previously read:

Proportion of subjects who achieve endoscopic improvement (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic improvement at Week 12.

Has been changed to read:

- Proportion of subjects who achieve endoscopic response (SES-CD > 50% from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 56 among subjects with endoscopic response at Week 12
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic remission at Week 12.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Eighth bullet previously read:

Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Baseline) at Week 56.

Has been changed to read:

Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 56.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Delete: fourteenth bullet

Change in IBDQ from Baseline at Week 56.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Twenty-third bullet previously read:

Change in IBDQ from Baseline at each scheduled visit in Maintenance Study.

Has been changed to read:

Change in IBDQ total score and individual IBDQ domain scores (bowel, emotional, social, systemic) from Baseline at each scheduled visit in Maintenance Study.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Twenty-eighth bullet previously read:

Change in Bristol Stool Scale score from Baseline at each scheduled visit in Maintenance Study.

Has been changed to read:

Change in Bristol Stool Chart score from Baseline at each scheduled visit in Maintenance Study.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Thirty-seventh and thirty-eighth bullet previously read:

- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 1.5 (and not worse than baseline) and average daily abdominal pain ≤ 1.0 (and not worse than baseline), at each scheduled visit in Maintenance Study.

- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline or average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline, at each scheduled visit in Maintenance Study.

Has been changed to read:

- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than baseline) and average daily abdominal pain ≤ 1.0 (and not worse than baseline), at each scheduled visit in Maintenance Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.
- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline or average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline, at each scheduled visit in Maintenance Study among subjects with Baseline SF ≥ 4.0 and/or AP ≥ 2.0.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Add: new forty-second and forty-third bullet

- Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at each scheduled visit in Maintenance Study.
- Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at each scheduled visit in Maintenance Study.

Section 5.3.3.3 Endpoints for Exploratory Maintenance Study
Add: new forty-fifth, forty-sixth, and forty-seventh bullet

- Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.

- Proportion of subjects who achieve endoscopic response (decrease > 50% SES-CD from Baseline [or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline]) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.

Section 5.5.1 Treatments Administered
Third paragraph, second and third sentence previously read:

The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and endoscopic response status (decrease in SES-CD > 50% from Baseline) per the site investigator reading at Week 12. Among Week 12 endoscopic responders, the randomization will be further stratified by endoscopic improvement, defined as achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Has been changed to read:

The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12 and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Section 5.5.2.2 Storage and Disposition of Study Drugs
Second paragraph, first sentence previously read:

Malfunctions or any temperature excursion must be reported to the Sponsor immediately.

Has been changed to read:

Malfunctions or any temperature excursion lasting longer than 30 minutes must be reported to the Sponsor immediately.

Section 6.1.5 Adverse Event Reporting
"Primary Study Designated Physician:" previously read:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Has been changed to read:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Section 7.0 Protocol Deviations
"Alternate Contact:" previously read:

[redacted]
GPRD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

Has been changed to read:

[redacted]
GPRD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

Section 8.1.4.1 Primary Efficacy Variable for Induction Study
First paragraph previously read:

The co-primary efficacy variables for Induction Study are proportion of subjects with moderately to severely active CD that have achieved clinical remission, defined as CDAI < 150, at Week 4 and proportion of subjects that have achieved endoscopic improvement, defined as an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable at Week 12.

Has been changed to read:

The co-primary efficacy variables for Induction Study are proportion of subjects with moderately to severely active CD that have achieved clinical remission, defined as CDAI < 150, at Week 4 and proportion of subjects that have achieved endoscopic response, defined as a decrease > 50% SES-CD from Baseline (or for a Baseline SES-CD of 4, at least a 2 point reduction from Baseline) at Week 12.

Section 8.1.4.1 Primary Efficacy Variable for Induction Study
Third paragraph, last sentence previously read:

For Week 12 endoscopic improvement, LOCF and OC will be used as sensitivity analyses.

Has been changed to read:

For Week 12 endoscopic response, OC will be used as sensitivity analysis.

Section 8.1.5 Statistical Analyses of Safety
Third paragraph, second sentence previously read:

An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 15.1 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.

Has been changed to read:

An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 20.1 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.

Section 8.1.5 Statistical Analyses of Safety
Third paragraph
Delete: last sentence

Treatment group differences in the overall incidence of treatment-emergent AEs will be assessed with Fisher's exact test for each preferred term.

Section 8.1.7 Interim Analysis
Previously read:

No interim analyses are planned.

Has been changed to read:

An interim analysis of the primary endpoint and ranked secondary efficacy variables for the Induction Study only as well as safety data collected from Baseline through double-blind Week 12 may be performed after the last subject in ITT population completes the 12-week double-blind Induction Study. A database cut will be performed and any discrepant data will be clarified before the lock. Since this interim analysis is the only and final analysis of the co-primary efficacy endpoints of the Induction Study, multiplicity adjustment is deemed not necessary.

Section 8.2 Determination of Sample Size
First paragraph, last sentence previously read:

A sample size of 600 (360 higher dose and 240 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Has been changed to read:

A sample size of 500 (300 higher dose and 200 standard dose) will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 4 between the dosing regimens using Fisher's exact test with 99% power at a 0.05 two-sided significant level.

Section 8.2 Determination of Sample Size
Second and third paragraph previously read:

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts a ~50% increase in the proportion of subjects with endoscopic improvement is expected. The observed rate of SES-CD ≤ 4 in Study M05-769 in subjects with Baseline SES-CD > 6 was 37% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate for SES-CD ≤ 4 using the higher induction regimen is 55%. A sample size

of 600 subjects (360 higher induction regimen and 240 standard induction regimen) will be adequate to detect at least an 18% treatment difference in endoscopic improvement rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 98% power at a 0.05 two-sided significance level.

Since the clinical remission at Week 4 endpoint and the endoscopic improvement at Week 12 endpoint are likely not independent of each other, the power for the co-primary endpoints for the study is expected to be > 97%.

Has been changed to read:

Since exposure/endoscopic relationships are not currently available for adalimumab, clinical remission will be based on PK/PD modeling which predicts a ~50% increase in the proportion of subjects with endoscopic response is expected. The observed rate of endoscopic response in Study M05-769 was 44% at Week 12 with the currently approved dosing regimen. Thus, by extrapolation, the expected rate endoscopic response at Week 12 using the higher induction regimen is 66%. A sample size of 500 subjects (300 higher induction regimen and 200 standard induction regimen) will be adequate to detect at least an 22% treatment difference in endoscopic response rates at Week 12 between the dosing regimens using Fisher's exact test with approximately 99% power at a 0.05 two-sided significance level.

Since the clinical remission at Week 4 endpoint and the endoscopic response at Week 12 endpoint are likely not independent of each other, the power for the co-primary endpoints for the study is expected to be > 98%.

Section 8.3 Randomization Methods
Second paragraph, second and third sentence previously read:

The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12, and endoscopic response status (decrease in SES-CD > 50% from Baseline) per the site investigator reading at Week 12. Among Week 12 endoscopic responders, the randomization will be further stratified by

endoscopic improvement, defined as achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Has been changed to read:

The re-randomization at Week 12 will be stratified by induction treatment regimen, clinical response (CR-70) status at Week 12, and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization will be further stratified by achievement of an SES-CD ≤ 4 and at least a 2 point reduction versus baseline and no subscore greater than 1 in any individual variable using the Week 12 SES-CD value provided by the site.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Statistics
		Bioanalysis
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Statistics
		Bioanalysis
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical