1.0 Title Page

Clinical Study Protocol M14-033

A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

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

AbbVie Investigational Product:	Adalimumab
Date:	16 June 2016
Development Phase:	3
Study Design:	This is a double-blind, randomized, multicenter study of higher versus standard adalimumab dosing regimens for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis.
EudraCT Number:	2013-001682-16
Investigator:	Multicenter: Investigator information is on file at AbbVie
Sponsor:*	**For non-EU Countries, Excluding Japan:** AbbVie 1 North Waukegan Rd. North Chicago, IL 60064 USA **For EU Countries:** AbbVie Deutschland GmbH & Co. KG Knollstrasse Ludwigshafen 67061 Germany **Japan:** AbbVie GK 3-5-27, Mita, Minato-ku Tokyo 108-6302, Japan

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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.

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	11 December 2013
Administrative Change 1	21 March 2014
Amendment 1	02 June 2014
Administrative Change 2	02 December 2014
Administrative Change 3	29 May 2015
Amendment 2	03 December 2015

The purpose of this Amendment is to:

- Section 1.0, Title Page, Section 6.1.5, Adverse Event Reporting, Section 7.0, Protocol Deviations, Appendix K, Japan Sub-Study, Section 6.1.5, Adverse Event Reporting, Change in SDP title and Department name

  Rationale: *Company updates*
- Section 1.0, Title Page, Section 6.1.5, Adverse Event Reporting, Change in Secondary Japan Contact

  Rationale: *Company updates*
- Section 1.2, Synopsis, updated to match with protocol changes

  Rationale: *Align with study changes*
- Section 1.2, Synopsis, Section 8.1.4.1, Primary Efficacy Variables, Appendix K, Japan Sub-Study, Section 8.1.4.1, Primary Efficacy Variables, typo correction from CRP to hs-CRP

  Rationale: *Typo correction*
- Section 1.3, List of Abbreviations and Definition of Terms, Section 8.1.4.1, Primary Efficacy Variables, Section 8.1.4.2, Secondary Efficacy Variables, Section 8.1.7, Interim Analysis, Appendix K, Japan Sub-Study, Section 8.1, Statistical and Analytical Plans, Section 8.1.1, Analysis Population, Section 8.1.3, Demographics and Baseline Characteristics, Section 8.1.4.1, Primary Efficacy Variables, Section 8.1.4.2, Secondary Efficacy Variables,

updated to include updated names of statistical groups due to statistical changes in protocol

Rationale: *Align with study changes*

- Section 1.3, List of Abbreviations and Definition of Terms, updated to include three (3) additional abbreviations.

  Rationale: *For consistency of section*

- Section 1.3, List of Abbreviations and Definition of Terms, updated to include three (3) additional definitions

  Rationale: *For clarification purposes*

- Section 3.0, Introduction, Section 3.1, Differences Statement, Section 5.1, Overall Study Design and Plan: Description, Table 1, TDM Arm Dose Adjustment Criteria, Section 5.3.4, Pharmacokinetic Variables, Section 5.5.1, Treatments Administered, Section 5.5.3, Method of Assigning Subjects to Treatment Regimens, Section 5.6.1, Discussion of Study Design and Choice of Control Regimens, Section 5.6.4, Selection of Doses in the Study, Section 8.1.1, Analysis Population, Section 8.1.3, Demographics and Baseline Characteristics, Section 8.1.7, Interim Analysis, Section 8.1.8, Pharmacokinetic Analyses, Section 8.2, Determination of Sample Size, Section 8.3, Randomization Methods, Appendix K, Japan Sub-Study, Section 5.1 Overall Study Design and Plan: Description, Table 2, Study Activities, Section 5.5.1, Treatments Administered, Section 5.5.3, Method of Assigning Subjects to Treatment Regimens, Section 8.1.3, Demographics and Baseline Characteristics, Section, 8.1.4.1 Primary Efficacy Variables, Section 8.3, Randomization Methods, Section 8.2, Determination of Sample Size, updated terminology from "arm" to "regimen," "dosing regimen" or "treatment group" as appropriate and introduce terminology Induction Study and Maintenance Study

  Rationale: *Align with study changes*

- Section 3.0, Introduction, Section 3.1, Differences Statement, Section 5.1, Overall Study Design and Plan: Description, Appendix K, Japan Sub-Study, Section 5.1, Overall Study Design and Plan: Description, Added clarification that both main and sub study have an Induction Study and a Maintenance Study.

Rationale: *Align with study changes*

- Section 4.0, Study Objective, Section 5.6.1, Discussion of Study Design and Choice of Control Regimens, Appendix K, Japan Sub-Study, Section 4.0, Study Objective of Japan Sub-Study, removed "primary"

  Rationale: *Align with study changes*

- Section 5.1, Overall Study Design and Plan: Description, Figure 1, Study Schematic, Section 5.2, Selection of Study Population, Section 8.2, Determination of Sample Size, Appendix K, Japan Sub-Study, Section 5.1, Overall Study Design and Plan: Description, Appendix K, Japan Sub-Study, Study Schematic, Appendix K, Japan Sub-Study, Section 8.2, Determination of Sample Size, updated with new study enrollment numbers

  Rationale: *Align with study changes*

- Section 5.1, Overall Study Design and Plan: Description, added language to clarify collection of PG sample

  Rationale: *To align with protocol changes made in Amendment 2*

- Section 5.1, Overall Study Design and Plan: Description, Figure 1, Study Schematic, Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 2, Study Activities, Appendix K, Japan Sub-Study, Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 2, Study Activities, Updates throughout protocol to note terminology change from "Period" to "Study"

  Rationale: *Align with study changes*

- Section 5.1, Overall Study Design and Plan, 8-Week Double-Blind Induction Study, clarified corticosteroid language

  Rationale: *updated for consistency with rest of protocol*

- Section 5.1, Overall Study Design and Plan: Description, Table 1, TDM Arm Dose Adjustment Criteria, added clarification to serum concentration in TDM regimen to mean adalimumab serum concentration

  Rationale: *For clarification purposes*

- Section 5.2.2, Exclusion Criteria, Exclusion Criteria 25, Section 5.3.1.1, Study Procedures, Hepatitis B Testing, Appendix K, Japan Sub-Study, Section 5.2.2,

Exclusion Criteria, added clarification to the results when testing for hepatitis B surface antibody

Rationale: *Due to changes in central laboratory*

- Section 5.2, Selection of Study Population, updated to convey that 840 subjects will be enrolled at up to 125 sites in the Main Study sites

  Rationale: *For clarification purposes*

- Section 5.3.2, Drug Concentration Measurements and Appendix K, Japan Sub-Study, Section 5.3.2, Drug Concentration Measurements, updates made to total number of PK samples

  Rationale: *Updated to reflect new enrollment numbers*

- Section 5.2.3.2, Concomitant Therapy, clarified assessment rules

  Rationale: *The study now has 2 distinct studies, each with its own endpoints; this re-wording removes ambiguity*

- Section 5.3.1.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 2, Study Activities, Appendix K, Japan Sub-Study, Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 2, Study Activities, footnote "j." expanded to remind sites to refer to the Lab Manual for this process.

  Rationale: *For clarification purposes*

- Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 2, Study Activities, Appendix K, Japan Sub-Study, Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, Table 2, Study Activities, footnote "m." added language to match the rest of the protocol.

  Rationale: *For consistency throughout protocol*

- Section 5.3.1.1, Study Procedures, TB Screening, For the PPD Test, language added to clarify how previous TB medications should be collected and added to the eCRF.

  Rationale: *For clarification purposes*

- Section 5.3.2.3, Disposition of Samples, removed the word "onsite"

  Rationale: *typo correction*

- Section 5.3.3.1, Primary Variables, Section 8.1.4.1, Primary Efficacy Variable, primary variables explained for Induction Study and Maintenance Study

  Rationale: *To reflect that the study now has 2 distinct studies that each have their own endpoints*

- Section 5.3.3.2, Secondary Variables, Section 8.1.4.2, Secondary Efficacy Variables, variables updated for Induction Study and Maintenance Study

  Rationale: *To reflect that the study now has 2 distinct studies that each have their own endpoints*

- Section 5.3.3.3, Additional Variables, variables updated for Induction Study and Maintenance Study

  Rationale: *To reflect that the study now has 2 distinct studies that each have their own endpoints*

- Section 5.5.1, Treatments Administered, Appendix K, Japan Sub-Study, Section 5.5.1, Treatments Administered, updated to reflect Week 52 or Premature Discontinuation

  Rationale: *For clarification purposes*

- Section 5.5.4, Selection and Time of Dose for Each Subject and Section 5.5.6, Treatment Compliance, clarified this instruction is for home dosing

  Rationale: *For clarification purposes*

- Section 6.1.4, Adverse Event Reporting, added clarification that medications for AEs/SAEs should be collected during 70-day follow-up phone call and that all 70-day follow-up phone call data is to be entered in the eCRF and recorded in source documentation

  Rationale: *For clarification purposes*

- Section 6.1.5, Adverse Event Reporting, Appendix K, Japan Sub-Study, Section 6.1.5, Adverse Event Reporting – update department number for Safety Team

  Rationale: *Company changes*

- Section 8.1, Statistical and Analytical Plans, additional information added on the Safety Analysis Plan between the main and sub studies.

  Rationale: *For clarification purposes*

- Section 8.1.4.1, Primary Efficacy Variables, Appendix K, Japan Sub-Study, Section 8.1.4.1, typo correction from IMM to Immunosuppressant

  Rationale: *Typo correction*
- Section 8.1.4.1, Primary Efficacy Variables, Appendix K, Japan Sub-Study, Section 8.1.4.1, Added language about the method and interpretation between the dosing regimens.

  Rationale: *To reflect that the study now has 2 distinct studies, each with its own set of endpoints.*
- Section 8.1.5, Statistical Analyses of Safety, Clarified statistical analysis delineating between Induction and Maintenance Studies.

  Rationale: *To reflect that the study now has 2 distinct studies*
- Section 8.1.7, Interim Analyses, updated noting that interim analysis may be performed via a database cut

  Rationale: *To more accurately reflect a possibility to perform an interim analysis and clarify the process*
- Section 8.2, Determination of Sample Size, updated to provide scientific justification of the increase in the number of patients

  Rationale: *To provide scientific justification of the increase in the number of patients*
- Section 8.2, Determination of Sample Size, Appendix K, Japan Sub-Study, Section 8.2, Determination of Sample Size, updated power of statistical analyses

  Rationale: *Sample size increased to reflect the lower than expected rate in a blinded review of Week 8 response status, and to increase the power for the primary endpoint at Week 52 which is previously a secondary endpoint.*
- Section 11.0, Data Quality Assurance, updated section to give more detail per standard language

  Rationale: *For clarification purposes*
- Appendix B, List of Protocol Signatories, updated per current study team

  Rationale: *Study team changes*

- Appendix J, 70-Day Follow-Up Phone Call, Sample updated to collect date of last study drug administration, collect reason if 70-day follow-up call was not performed, and add additional help text

  Rationale: *To reduce site confusion in completing the form and facilitate whether further follow-up is required*
- Appendix K, Japan Sub-Study, Section 8.1.2, Planned Methods of Statistical Analysis, deleted

  Rationale: *The information was the same in the main study Section 8.1.2 so Appendix K Section 8.1.2 was redundant*
- Appendix K, Japan Sub-Study, Section 8.1.7, Interim Analyses, updated noting that interim analysis will be performed only if performed for the main study

  Rationale: *To more accurately reflect a possibility to perform an interim analysis*

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

1.2 Synopsis

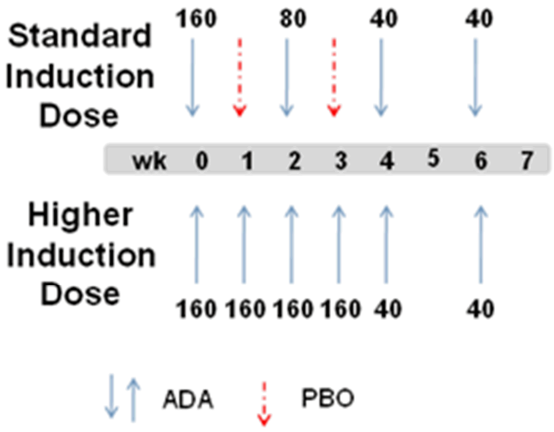
AbbVie Inc.	**Protocol Number:** M14-033
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 16 June 2016
Protocol Title: A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis	
Objective: The objective is to evaluate safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active Ulcerative Colitis (UC).	
Investigators: Multicenter Trial (Investigator information on file at AbbVie).	
Study Sites: Approximately 125 sites for the main study and approximately 21 sites for the Japan sub-study.	
Study Population: Male and female subjects ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active UC (up to 25% infliximab-experienced).	
Number of Subjects to be Enrolled: For the main Induction Study, approximately 840 subjects (504 subjects in the higher induction dose regimen and 336 subjects in the standard induction dose regimen) will be enrolled at approximately 125 sites worldwide. All subjects who complete the Induction Study (regardless of achievement of response at Week 8) will continue into the Maintenance Study. An additional 100 Japanese subjects (60 in the higher induction dose regimen and 40 in the standard induction dose regimen) in a Japan sub-study will be enrolled at 21 Japan sites. In both the main study and Japan sub study, up to 25% of subjects with previous infliximab exposure may be enrolled.	
Methodology: This Phase 3 study design includes the Screening Period followed by an 8-Week double blind Induction Study and a 44-Week double blind Maintenance Study. The Induction Study: will evaluate the efficacy and safety of a higher induction dosing regimen of adalimumab versus standard induction dosing in inducing clinical remission at Week 8 in subjects with moderately to severely active UC. The Maintenance Study: will evaluate the safety and efficacy of 44 weeks of three maintenance dosing regimens of adalimumab in achieving clinical remission at Week 52 (from the Induction Study Baseline) in subjects with moderately to severely active UC who achieved clinical response at Week 8 of the Induction Study.	

Methodology (Continued):

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 8 will represent the final assessment in the Induction Study. Week 52 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study). Subjects will have moderately to severely active UC as defined by a Mayo Score of 6 to 12 points with an endoscopy subscore of 2 or 3, confirmed by a central reader. For all Mayo Score evaluations throughout the entire study, the stool frequency and the rectal bleeding subscores will be calculated based on entries recorded into the subject's diary.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the Induction Study. During the Induction Study, subjects will be randomized at Baseline to one of 2 double-blinded adalimumab induction regimens (higher dose or standard dose) in a 3:2 ratio, as shown in the following figure. Use of the 3:2 randomization scheme allows for collection of additional safety data with the higher induction dose regimen. The randomization will be stratified by previous infliximab use and Baseline corticosteroid use.

8-Week Double-Blind Induction Study



The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6 leads to a total adalimumab dose over 8 weeks that is approximately twice that of the standard induction dose regimen (720 mg versus 320 mg). The higher induction dose regimen was designed for rapid attainment of higher adalimumab serum concentrations in order to rapidly control inflammation. Pre dosing serum samples for infliximab concentration and human antichimeric antibodies (HACAs) will be collected at Week 0. Pre-dosing serum samples for adalimumab drug levels will be collected at Weeks 0, 2, 4, and 8. Pre-dosing serum samples for anti-adalimumab antibodies will be collected at Weeks 0, 4, and 8.

Methodology (Continued):

At Week 4, all subjects who are taking oral corticosteroids from Baseline will have their corticosteroid therapy tapered according to the proposed tapering schedule specified in the 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.

At the conclusion of the 8-Week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study. Re-randomization into the Maintenance Study will be stratified by induction treatment regimen in the Induction Study and response status (per Full Mayo Score) at Week 8. Among the responders at Week 8, the re-randomization will be further stratified by remission status (per Full Mayo score) at Week 8. All subjects in the main study who complete the Induction Study) will be re-randomized into one of three blinded treatment groups in a 2:2:1 ratio:

- Adalimumab 40 mg every other week (eow)
- Adalimumab 40 mg every week (ew)
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory)*

* 1) All subjects in the TDM dosing regimen will receive 40 mg eow at Week 8 and Week 10. At Weeks 12, 24, and 37, the regimen will be adjusted for subjects meeting the dose adjustment criteria (see table below) based on blinded serum concentrations at the prior visit (Weeks 10, 22 and 35, respectively) and rectal bleeding subscore at the prior and current visits as follows:

- Subjects receiving 40 mg eow who meet the dose adjustment criteria will escalate to 40 mg weekly.
- Subjects receiving 40 mg ew who meet the dose adjustment criteria will receive a one-time dose of 160 mg at the visit, and resume 40 mg ew starting the following week.

2) Japan sub-study does not have TDM dosing regimen. Subjects will be re-randomized into Adalimumab 40 mg eow treatment group or Adalimumab 40 mg ew treatment group in a 1:1 ratio.

Pre-dosing serum samples for adalimumab drug levels will be collected in all subjects at Weeks 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52/Premature Discontinuation (PD), and unscheduled visits. Pre-dosing serum samples for anti-adalimumab antibodies will be collected at Weeks 12, 24, 37, 52/PD, and unscheduled visits.

The goal of the TDM dosing regimen is to attain serum adalimumab levels within a targeted concentration range (selected based on exposure-response analyses from Study M06-827) while avoiding excessively high concentrations. During maintenance therapy in Study M06-827, concentrations ranged from 0 to 39.3 µg/mL with eow dosing and 0 to 38.0 µg/mL with ew dosing. The lower bound (10 µg/mL) of the targeted concentration range for the TDM dosing regimen is similar to the median concentrations observed over time for the subjects in remission at Week 52 of Study M06-827 (11.4, 10.6, and 10.8 µg/mL, for Weeks 8, 32, and 52, respectively). Use of this concentration as the minimum threshold to trigger dose escalation will lead to the majority of subjects achieving concentrations greater than 10 µg/mL. Since serum adalimumab concentrations roughly double with a doubling of dose, an upper bound of 20 µg/mL is expected to achieve maximal trough concentrations in the range of the highest trough concentrations observed in Study M06-827. It is expected that approximately 60% of subjects in the TDM dosing regimen will escalate to ew dosing and 15% or fewer will receive reinduction using this concentration range plus the Rectal Bleeding Subscore (RBS) criteria outlined in the table below as a guide to adjust adalimumab dosing.

Methodology (Continued):

TDM Dose Adjustment Criteria[a]

Adalimumab Serum Concentration[b]	Rectal Bleeding Subscore[c]	Dose Escalate?[d]
< 10 µg/mL	Any	Yes
10 µg/ml to 20 µg/mL	< 1	No
10 µg/ml to 20 µg/mL	≥ 1	Yes
> 20 µg/mL	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. The score entries into the subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding Subscore for each study visit.

d. For subjects on 40 mg eow, escalate to 40 mg ew. Subjects on 40 mg ew will receive "reinduction" with a dose of 160 mg at the visit and resume 40 mg ew 1 week later.

Note: There will be no allowance for dose adjustment in the adalimumab eow or ew dosing regimens.

Study visits for clinical and safety assessments will be performed at Baseline (Week 0), Weeks 1, 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, and 52/PD. All subjects will be provided with a Subject Diary where they will record ulcerative colitis-related symptoms (daily stool frequency, abdominal discomfort, number of bloody stools, fecal urgency, and general well-being), use of anti-diarrheals, use of medications for endoscopy preparation, and study drug dosing information throughout the study. Blood samples will be collected for hs-CRP, adalimumab serum concentrations, anti-adalimumab antibody (AAA) levels, and other biomarker analyses. In addition, stool samples for calprotectin and microbiota metagenomic analyses will be collected. The stool samples should be taken before starting bowel preparations for endoscopy. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy for histologic assessment during Screening, at Week 8 and at Week 52/PD (for subjects who remain in the study through at least Week 24) with local investigator assessment for Mayo endoscopic subscore confirmed by a central reader. The central reviewer scoring will be used for all efficacy assessments. The endoscopy subscore result from the central reviewer during the screening period will be used to evaluate the eligibility of a subject to enroll in the study.

Subjects who consent to participate in the optional pharmacogenetic (PG) analysis should have an additional blood sample drawn at Baseline and at Week 52/PD. If the sample is not collected at Baseline, preferably it should be collected at the next study visit.

Subjects will be discontinued if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator. Subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable should contact the Study Designated Physician.

Methodology (Continued):

Subjects will only be allowed to change the dosage of UC-specific concomitant medications as specified below:

- At Week 4, all subjects who are taking oral corticosteroids from Baseline will have their corticosteroid therapy tapered according to the proposed tapering schedule specified in the Protocol. 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.
- 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.

Subjects in whom UC-related medications (defined as oral or rectal aminosalicylates, systemic or rectal corticosteroids, or systemic medications affecting the immune system, including thiopurines, MTX, and agents listed in the study exclusion criteria) 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.

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

Diagnosis and Main Criteria for Inclusion/Exclusion:

The following Inclusion/Exclusion criteria are for subjects enrolled in the main study. Separate Inclusion/Exclusion criteria for subjects recruited in Japan will be followed in the Japan sub-study.

Main Inclusion:

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
2. Male or female ≥ 18 and ≤ 75 years of age at the Baseline visit.
3. Subject with a diagnosis of UC for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period, with exclusion of current infection, dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.

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

Main Inclusion (Continued):

4. Active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) 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 or immunosuppressants as defined below):
   - Subject taking oral corticosteroids, excluding budesonide or beclomethasone:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subject 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 subject 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 subject 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 subject 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.
   - Subject taking oral beclomethasone:
     - Dose must not exceed 5 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.

   or,
   - At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP) or injectable methotrexate (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 dosing and duration of use criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline), however prior or current 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.

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

Main Inclusion (Continued):

5. Subject may be included if they have previously experienced a benefit for their UC from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of UC related symptoms) or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly 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);
   - A 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.
7. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.
8. Subject has a negative tuberculosis (TB) Screening Assessment. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.
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, chest x-ray, 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 diagnosis and/or history of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
7. Positive pregnancy test at Screening (serum) or Baseline (urine).
8. Female who is breast-feeding or considering becoming pregnant during the study.

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

Main Exclusion (Continued):

9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subject on azathioprine, 6-MP, 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.
11. Subject on oral aminosalicylates who:
    - Has not been on stable doses of these medications for at least 14 days prior to Baseline; or
    - Has discontinued use of aminosalicylates within 14 days of Baseline.
12. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subject on oral budesonide > 9 mg/day; or subject on oral beclomethasone > 5 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 of at least 14 days in duration 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 oral 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 of at least 14 days in duration 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 has **not** been a current steroid course of at least 14 days in duration prior to Baseline; or
    - Subject taking oral beclomethasone:
      - has **not** been on a stable dose for at least 7 days prior to Baseline; or
      - but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline; or

    Has been taking both oral budesonide (or oral beclomethasone) and oral prednisone (or equivalent) simultaneously

    and/or

    Has discontinued use of corticosteroids within 14 days of Baseline.
13. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
14. Positive Clostridium difficile *(C. difficile)* toxin stool assay during the Screening Period.
15. Currently receiving total parenteral nutrition (TPN).

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

Main Exclusion (Continued):

16. Subject who received any investigational agent or procedure (including previous fecal microbial transplantation) within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer.
17. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
18. 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.
19. 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®]) or previous participation in an adalimumab clinical study. Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including but not limited to adalimumab [Humira®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).
20. Subject with known hypersensitivity to the excipients of adalimumab (see Protocol).
21. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
22. 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. If the Screening endoscopy shows evidence of current dysplasia or malignancy, subject may not be enrolled in the study.
23. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).
24. Subject with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
25. 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.

26. Chronic recurring infections or active TB.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** 27. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and/or any other condition which would put the subject at risk by participation in the study. 28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study. 29. 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.	
Investigational Products:	Adalimumab
Induction Study: **Double-Blind Induction Doses:** NOTE: In order to retain blinding, all subjects in the Standard Induction Dose Regimen will receive matching placebo injections in addition to the adalimumab injection at Weeks 1, 2 and 3.	Subjects will be randomized to receive one of 2 double-blind adalimumab induction dosing regimens. Standard Induction Dose Regimen: 160 mg at Week 0 and matching placebo at Week 1. Subjects will receive 80 mg at Week 2 and matching placebo at Week 3. Subjects will receive 40 mg at Week 4 and Week 6. Higher Induction Dose Regimen: 160 mg at Weeks 0, 1, 2, and 3. Subjects will receive 40 mg at Week 4 and Week 6.

Maintenance Study: **Double-Blind Maintenance Doses:**	Subjects will be re-randomized to receive one of 3 double-blind adalimumab maintenance dosing regimens. Adalimumab 40 mg eow Regimen: 40 mg every other week, starting at Week 8 until Week 50. Matching Placebo will be administered every other week, starting at Week 9 until Week 51. No dose will be administered at Week 52. Adalimumab 40 mg ew Regimen: 40 mg every week, starting at Week 8 until Week 51. No dose will be administered at Week 52. Adalimumab TDM Regimen: 40 mg eow at Week 8 and Week 10. Matching placebo at Week 9 and Week 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria. Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly. Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week. Subjects receiving 40 mg eow who do not meet the regimen adjustment criteria will receive adalimumab 40 mg eow and placebo at alternative weeks. No dose will be administered at Week 52. NOTE: In order to retain blinding, all subjects in the 40 mg eow and 40 mg ew regimen groups and subjects who do not meet the criteria for dose escalation in the TDM regimen group will receive matching placebo injections in addition to the adalimumab injection (placebo reinduction) at Weeks 24 and 37.
Mode of Administration:	Subcutaneous injection (SC)

Duration of Treatment: The overall study treatment duration is 52 weeks (8 weeks of induction therapy during the Induction Study followed by 44 weeks of maintenance therapy during the Maintenance Study). There will be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely. The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

Criteria for Evaluation:

The following analysis is for subjects recruited in the main study. A separate statistical analysis will be performed for subjects recruited in the Japan sub-study and for all subjects recruited in the main study and the Japan sub-study.

Efficacy:

For the Induction Study endpoints, the subjects receiving the higher adalimumab induction dose regimen will be compared to subjects receiving the standard adalimumab induction dose regimen. For the Maintenance Study endpoints, the subjects receiving the eow regimen will be compared to subjects receiving the ew regimen. The TDM regimen will be used for exploratory analyses. For the primary endpoints, clinical remission or response will be evaluated using Full Mayo Score. Exploratory analysis will also be performed using Full Mayo Score excluding PGA (Adapted Mayo Score) and Full Mayo Score excluding Endoscopy Subscore (Partial Mayo Score).

Criteria for Evaluation (Continued):

Efficacy (Continued):

The primary efficacy endpoint for the Induction Study is:

- Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

- Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Induction Study are:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.
2. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.
3. Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 8.
4. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.
5. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.

Additional pre-specified endpoints in the Induction Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Induction Study
- All-cause and UC-related hospitalization and surgery rates during Weeks 0 – 8.
- Change from Baseline in histologic score at Week 8.
- Proportion of subjects achieving clinical remission per Adapted Mayo Score (defined as stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1) at Week 8.
- Proportion of subjects achieving Full Mayo score, excluding the PGA subscore, ≤ 2 with no subscore > 1 at Week 8.
- Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 8.
- Relationship between histologic scores and endoscopic subscore of 0 at Week 8.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Maintenance Study are:

1. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
2. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 90 days at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
4. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.

Criteria for Evaluation (Continued):

Efficacy (Continued):

5. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
7. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
8. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 52.
9. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
10. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
11. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
12. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

Additional pre-specified endpoints in the Maintenance Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Maintenance Study by Week 8 response status.
- Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic improvement at Week 52.
- All cause and UC-related hospitalization and surgery rates during Weeks 8 – 52.
- Change from Baseline in histologic score at Week 52.
- Proportion of Week 8 responders per Adapted Mayo Score (defined as decrease from Baseline in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1) achieving clinical remission per Adapted Mayo Scores at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) achieving Full Mayo score, excluding the PGA subscore, ≤ 2 with no subscore > 1 at Week 52.
- Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 52.
- Relationship between histologic scores and endoscopic subscore of 0 at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.

Criteria for Evaluation (Continued):

Efficacy (Continued):

The following additional pre-specified endpoints will also be analyzed in both the Induction Study and the Maintenance Study.

- Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.
- Proportion of subjects who are taking corticosteroids at Baseline and are steroid-free over time.
- Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.
- Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score ≤ 2 with no subscore > 1) score over time.
- Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of ≥ 2 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) over time.
- Change from Baseline in hs-CRP over time.
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in IBDQ score over time.
- Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.
- Change from Baseline in SF-36 score over time.
- Change from Baseline in fecal calprotectin over time.
- Time to achievement of remission (per Partial Mayo score).
- Time to achievement of response (per Partial Mayo score).
- Time to loss of response and factors associated with loss of response.
- Change in presence of extraintestinal manifestations over time.

Pharmacokinetics:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline and Weeks 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits. Pre-dosing serum samples for HACAs and infliximab concentrations will be collected at Week 0.

Blood samples will be collected for the measurement of AAA just prior to dosing at Baseline and Weeks 4, 8, 12, 24, 37, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits.

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:

The following statistical analysis plan is for subjects recruited in the main study. A separate statistical analysis plan will be provided for subjects recruited in the Japan sub-study and for all the subjects recruited in the main study and the Japan sub-study (See Appendix K).

Efficacy:

For the Induction Study, a total of 840 subjects will be allocated to the adalimumab higher induction dosing regimen and the adalimumab standard induction dosing regimen in a 3:2 ratio (504 and 336 subjects in each regimen, respectively). The sample size for the Induction Study is based on the expected proportions of subjects who achieve clinical remission at Week 8. Assuming the clinical remission rate of 35% in the adalimumab higher induction dosing regimen and 20% in the adalimumab standard induction dosing regimen at Week 8, this sample size will provide > 95% power to detect a difference of 15% between the two treatment groups for the primary endpoint of the Induction Study using two-sided Fisher's Exact test at a 0.05 significance level. The efficacy analysis will be based on intent-to-treat analysis set. The intent-to-treat analysis set includes all randomized subjects who receive at least one dose of study drug in the Induction Study 1 (ITT1). The difference between the higher induction dosing regimen group versus the standard induction dosing regimen group in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 8 endpoint. Subjects with missing Mayo score data at Week 8 will be classified as Week 8 non-responders for the Week 52 Maintenance Study analyses. As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint.

For the Maintenance Study, the sample size is based on the expected proportions of subjects who achieve clinical remission at Week 52. Assuming the average response rate at Week 8 in the Induction Study is 50%, a total of 420 Week 8 responders will be re-randomized to adalimumab 40 mg eow, adalimumab 40 mg ew, and TDM regimen in a ratio of 2:2:1; i.e., 168 subjects each in the eow and ew groups and 84 subjects in the TDM regimen. Assuming the Week 52 clinical remission rate of 48% in the ew group and 30% in the eow group among Week 8 responders, this sample size will provide 90% power to detect a treatment difference of 18% between the two groups using two-sided Fisher's Exact test at a 0.05 significance level. The efficacy analysis will be based on intent-to-treat analysis set. The intent-to-treat analysis set includes all re-randomized subjects who receive at least one dose of study drug in the Maintenance Study (ITT2). The difference between the adalimumab eow regimen versus the adalimumab ew regimen in the proportion of subjects achieving clinical remission at Week 52 among Week 8 responders will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for the induction treatment regimen dosing and remitter status at Week 8 (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site). A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 52 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 52 endpoint.

Statistical Methods (Continued):

Efficacy (Continued):

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint.

The secondary efficacy variables of the Induction Study and the Maintenance Study are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at an alpha level of 0.050 (two-sided) in ranked endpoint order until the significant level exceeds 0.05. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables. For the Induction Study Week 8 endpoints, the difference between the higher adalimumab induction dosing regimen versus the standard adalimumab induction dosing regimen will be assessed using ITT1 analysis set. For the Maintenance Study Week 52 endpoints, the difference between the eow group versus the ew group will be assessed using ITT2 analysis set. Categorical data will be described by frequency and percentage; continuous data will be described by mean, standard deviation, minimum, median, and maximum. In general, the secondary endpoints at Week 8 for the Induction Study that are of the binary type will be analyzed using a two-sided CMH test adjusted for previous infliximab use and Baseline corticosteroid use using the ITT1 analysis set, and the secondary endpoints at Week 52 for the Maintenance Study that are of the binary type will be analyzed using a two-sided CMH test adjusted for induction treatment regimen and remitter status (per Full Mayo score) at Week 8 (where applicable) using the ITT2 analysis set. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. Continuous secondary efficacy variables will be analyzed using Analysis of Covariance (ANCOVA) with factor for treatment group, stratification variables and Baseline values. NRI for missing data will be used for categorical endpoints. Procedures for handling missing data for continuous endpoints will be described in the Statistical Analysis Plan.

Pharmacokinetic:

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

Immunogenicity:

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

Safety:

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed for both Induction and Maintenance Studies using the safety analysis set, which includes all subjects who receive at least one dose of study medication in each Study, respectively. Treatment-emergent adverse events will be tabulated by system organ class and by MedDRA preferred term by treatment group for the Induction Study and the Maintenance Study, and for any adalimumab over the entire study. Mean changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AAA	Anti-adalimumab Antibody
ADA	Adalimumab
AE	Adverse event
ALT	Alanine Transaminase
ANA	Antinuclear Antibody
AST	Aspartate Transaminase
BCG	Bacillus Calmette-Guérin
BUN	Blood Urea Nitrogen
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
DNA	Deoxyribonucleic Acid
dsDNA	Double-stranded DNA
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EIMs	Extra-Intestinal Manifestations
eow	every other week
ew	every week
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HACA	Human Antichimeric Antibody
HBs Ab	Hepatitis B surface antibodies
HBs Ag	Hepatitis B surface antigen
HBc Ab	Hepatitis B core antibodies
HBV	Hepatitis B Virus

hs-CRP	high-sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
I-ITT1	Integrated Intent-To-Treat Induction Study
I-ITT2	Integrated Intent-To Treat Maintenance Study
IM	Intramuscular
IRB	Institutional Review Board
ITT1	Intent-To-Treat Induction Study
ITT2	Intent-to-Treat Maintenance Study
IRT	Interactive Response System
J-ITT1	Japan Integrated Intent-To-Treat Induction Study
J-ITT2	Japan Integrated Intent-To-Treat Maintenance Study
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTX	Methotrexate
PGA	Physician's Global Assessment
PA	Posteroanterior
PBO	Placebo
PD	Premature Discontinuation
PG	Pharmacogenetic
PK	Pharmacokinetics
POR	Proof of Receipt
PML	Progressive Multifocal Leukoencephalopathy
PMS	Partial Mayo Score
PPD	Purified Protein Derivative
RBS	Rectal Bleeding Subscore
SAE	Serious Adverse Event
SFS	Stool Frequency Subscore
SC	Subcutaneous
SDP	Study Designated Physician
TDM	Therapeutic Drug Monitoring
TB	Tuberculosis

TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
UC	Ulcerative Colitis
WPAI	Work Productivity and Impairment Questionnaire

Definition of Terms

Adapted Mayo Score	Full Mayo Score minus the Physician's Global Assessment (PGA)
Remission per Adapted Mayo Score	An Adapted Mayo Score ≤ 2, with stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
Remission per Full Mayo Score	A Full Mayo score ≤ 2 with no subscore > 1
Remission per Partial Mayo Score	A Partial Mayo score ≤ 2 with no subscore > 1
Response per Adapted Mayo Score	A decrease in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1
Response per Full Mayo Score	A decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1
Response per Partial Mayo Score	A decrease in Partial Mayo score ≥ 2 points and ≥ 30% from Baseline PLUS a decrease in the RBS ≥ 1 or an absolute RBS of 0 or 1
IBDQ Response	An increase of ≥ 16 points from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score
Endoscopic Improvement	Endoscopy subscore of 0 or 1

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3.0 Introduction

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease. It is postulated that UC is caused by unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals.[1] UC is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The incidence in North America is estimated at 2.2 to 14.3 cases per 100,000 person-years with a prevalence of 37 to 246 cases per 100,000 persons.[2] The burden of UC on the healthcare system is profound, accounting for nearly 500,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone.[3]

The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and remission. The diagnosis of UC is suspected on clinical grounds and supported by diagnostic testing, and elimination of infectious causes.[4]

The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extraintestinal complications include arthritis (sacroiliitis and ankylosing spondylitis), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.[5]

The aim of medical treatment in UC is to control inflammation and reduce symptoms. Available pharmaceutical therapies are limited, do not always completely abate the inflammatory process, and have significant adverse effects. Therapies for mildly to moderately active UC include 5-aminosalicylic acid (5-ASA) derivatives and immunosuppressants. Corticosteroids are used in patients with more severe symptoms but are not useful for longer term therapy.[6] The frequency and severity of corticosteroid toxicities are significant, including infections, emotional and psychiatric disturbances,

skin injury, and metabolic bone disease. Corticosteroids are not effective for the maintenance of remission and the UC practice guidelines from the American College of Gastroenterology recommend against chronic steroid treatment.[7]

Patients with moderate to severe symptoms may derive some benefits from immunomodulatory agents (azathioprine [AZA], 6-mercaptopurine [6-MP] or methotrexate [MTX]); however, the use of these agents is limited by slow onset of action (3 to 6 months) and adverse events (AEs), including bone marrow suppression, infections, hepatotoxicity, pancreatitis, and malignancies.[7,8] Removal of the colon/rectum can eliminate the source of the inflammatory process but may be accompanied by significant morbidity.

The safety and efficacy of adalimumab for the induction and maintenance of clinical remission in adult subjects with moderately to severely active UC has been studied in two completed clinical trials (Study M06-826 and Study M06-827) and an ongoing open-label study (Study M10-223).[9-11] In addition, adalimumab was associated with statistically significant and clinically relevant results in multiple other endpoints, including response, endoscopic improvement, and improvements in Inflammatory Bowel Disease Questionnaire (IBDQ) scores compared to placebo for up to 52 weeks in these subjects.[11]

The purpose of this study is to evaluate a higher induction and maintenance regimen, including an exploratory dosing regimen evaluating a therapeutic drug monitoring strategy, than the standard approved adalimumab induction regimen (160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every other week [eow] beginning at Week 4) for induction and maintenance therapy in adult patients with moderately to severely active ulcerative colitis. This study is designed to fulfill the following two post-marketing requirements (PMR) that were part of the US approval of adalimumab in adult patients with UC:

- PMR 5: *Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR 3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.*
- PMR 6: *A safety and pharmacokinetic trial as a sub-study of the trial described in PMR 5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR 3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.*

This study is constructed of a main study and a Japan sub-study. Both the main study and Japan sub-study include an Induction Study and a Maintenance Study. The protocol indicates the method for the main study and is to be followed for the Japan sub-study except as indicated in Appendix K.

3.1 Differences Statement

The differences between Study M14-033 and the other UC studies (Study M06-826 and Study M06-827), are the inclusion of a higher induction dose, a higher maintenance dose (weekly dosing) and an adjustable dosing regimen based on therapeutic drug monitoring during the Maintenance Study, which will allow for a greater range of exposure and ultimately provide greater precision around adalimumab dosing/exposure and

efficacy/safety relationships in subjects with moderately to severely active ulcerative colitis. The pharmacokinetic profile of adalimumab during Induction and Maintenance Studies and its relationship to efficacy in adult subjects with moderately to severely active ulcerative colitis will be characterized.

In addition, the methodology differs from the registration trials in that the endoscopy was not read centrally in the registration trials, and Study M06-827 included 40% of subjects previously treated with an anti-tumor necrosis factor (TNF) agent compared to a maximum of 25% in the present trial.

3.2 Benefits and Risks

Extensive clinical and postmarketing experience exists with adalimumab in a wide range of disease states, including Crohn's disease and UC. The safety profile of adalimumab in those indications is well-established with more than 50,000 patient-years of adalimumab clinical trial experience. The clinical studies in adult UC have not altered this safety profile and demonstrated a positive benefit/risk balance. Conditions which may present a risk specifically for patients with UC 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 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic

inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate) and serum cytokines rapidly decrease.

Adalimumab was first approved in US and EU for the treatment of Rheumatoid Arthritis in 2002 and 2003, respectively, and subsequently by the Pharmaceuticals and Medical Devices Agency in Japan in 2008. 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 the EU, 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 based on extensive postmarketing experience and continued clinical trial subject 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 subjects who are 30 years old or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your

attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event Reporting.

4.0 Study Objective

The study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, double-blind, randomized, multicenter study of higher versus standard adalimumab dosing regimens for induction and maintenance therapy in subjects with moderately to severely active UC (Mayo Score of 6 to 12 points with an endoscopy subscore of 2 or 3, confirmed by a central reader). For all Mayo Score evaluations throughout the study, the stool frequency and the rectal bleeding subscore will be calculated according to Appendix C.

The study was designed to enroll 840 subjects in the main study (504 subjects in the higher induction dose regimen and 336 subjects in the standard induction dose regimen) at approximately 125 sites worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. There also will be 100 Japanese subjects (60 subjects in the higher induction dose regimen and 40 subjects in the standard induction dose regimen) in a Japan sub-study to be enrolled at 21 Japan sites. The Japan sub-study will be conducted utilizing the same design as outlined in the main study with the exceptions that are outlined in Appendix K. If the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

This study will include:

- A 3-Week Screening Period

- An 8-Week Double-Blind Induction Study
- A 44-Week Double-Blind Maintenance Study
- A 70-Day Follow-Up Period

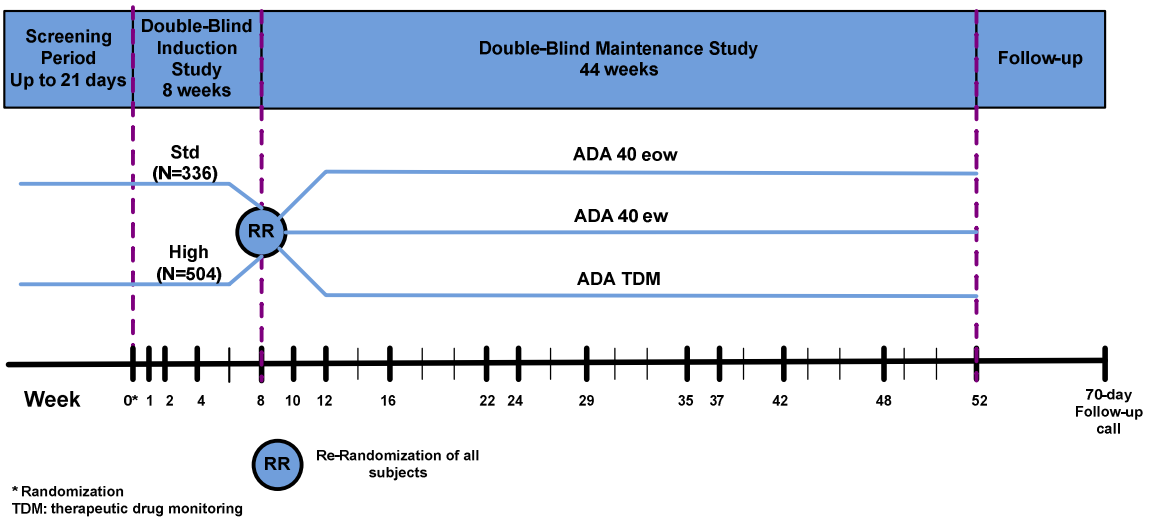
During both the Induction Study and the Maintenance Study, visit week designations will represent weeks since first dose in the Induction Study. Week 0 (Baseline) will reflect the date of first adalimumab dosing in the Induction Study. Week 8 will represent the final assessment in the Induction Study and the beginning of the Maintenance Study. Week 52 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study). A subject's participation in the study is anticipated to be up to 65 weeks. There is a ± 3-day window for all study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

Study visits for clinical and safety assessments will be performed at Baseline (Week 0), Weeks 1, 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48 and 52/PD. All subjects will be provided with a subject diary at Screening where they will record ulcerative colitis-related symptoms (stool frequency, abdominal discomfort, number of bloody stools, fecal urgency, and general well-being), use of anti-diarrheals, use of medications for endoscopy preparation, and study drug dosing information) throughout the study. Blood samples will be collected for high-sensitivity C-reactive protein (hs-CRP), adalimumab serum concentrations, anti-adalimumab antibody (AAA) levels, and other biomarker analyses as indicated in Table 2. In addition, stool samples for calprotectin, and microbiota metagenomic analyses will be collected. The stool samples should be taken before starting bowel preparations for endoscopy. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy for histologic assessment during Screening, at Week 8 and Week 52/PD (for subjects who remain in the study through at least Week 24), with local investigator assessment for Mayo endoscopic subscore confirmed by a central reader. Subjects who consent to participate in the optional pharmacogenetic (PG) analysis should have an additional blood sample drawn at Baseline

and at Week 52/PD. If the sample is not collected at Baseline, it should be collected at the next study visit.

A schematic of the study design is presented in Figure 1.

Figure 1. Study Schematic



Screening Period

The Screening Period begins at the Screening Visit and continues through to Baseline Visit (Week 0). Screening Assessments will include medical history, physical examination, chest x-ray, endoscopy (colonoscopy or flexible sigmoidoscopy), electrocardiogram (ECG), diary review and laboratory results including pregnancy testing, all of which will be reviewed by the study site to confirm selection criteria are met prior to enrolling the subject.

Subjects who meet all eligibility criteria during the Screening Period (refer to Section 5.2.1) will enter the 8-Week Double-Blind Induction Study. The length of time between screening and the 8-Week Double-Blind Induction Study Baseline Visit must allow time for endoscopy central reading and lab results. The Screening period

(1 – 3 weeks, ±3 days is granted around all study visits) 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).

Subjects who initially screen fail for the study may be permitted to re-screen following re-consent. There is no minimum period of time a subject must wait to re-screen for the study. 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. 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, and ECG, these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed. An endoscopy 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 30 days have passed between the endoscopy date and the rescreening date. All other screening procedures will be repeated. As appropriate, sites should contact the AbbVie SDP to confirm if subjects may be re-screened.

8-Week Double-Blind Induction Study

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the 8-Week Induction Study. In both the main study and the Japan sub-study populations, up to 25% of subjects with previous infliximab exposure may be enrolled.

Subjects will be randomized via interactive response system (IRT) at Baseline (Week 0) to one of 2 double-blinded adalimumab induction regimens (higher dose or standard dose) in a 3:2 ratio. Use of the 3:2 randomization scheme allows for collection of additional safety data with the higher induction dose regimen. The randomization will be stratified by:

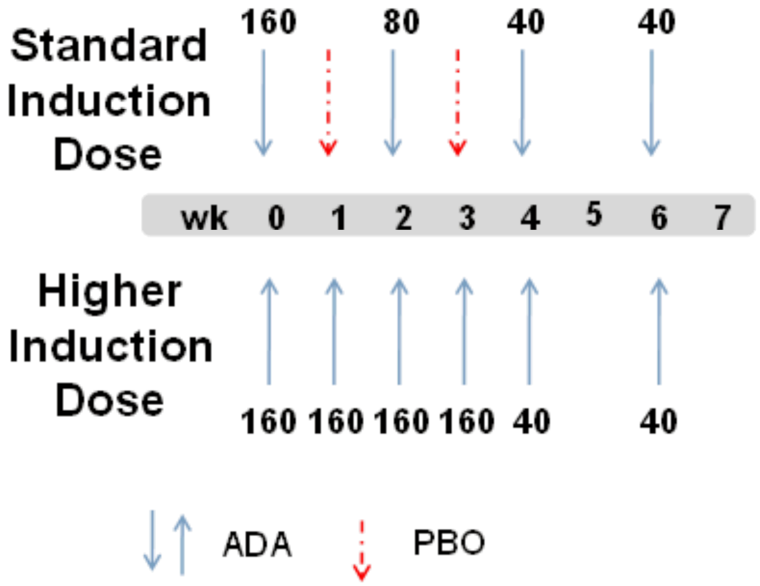
- Previous infliximab use

and

- Baseline corticosteroid use.

The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6 leads to a total adalimumab dose over 8 weeks that is approximately twice that of the standard induction regimen (720 mg versus 320 mg) as shown in Figure 2 below.

Figure 2. 8-Week Double-Blind Induction Study



Subjects will return to the study site at scheduled visits and complete study procedures for each visit as outlined in Section 5.3.1.1.

At Week 4, all subjects who are on oral corticosteroids from Baseline will have their corticosteroid dose tapered according to the proposed tapering schedule outlined in the protocol. 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.

44-Week Double-Blind Maintenance Study

At the conclusion of the 8-Week Double-Blind Induction Study, subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Study to one of three treatment groups in a 2:2:1 ratio:

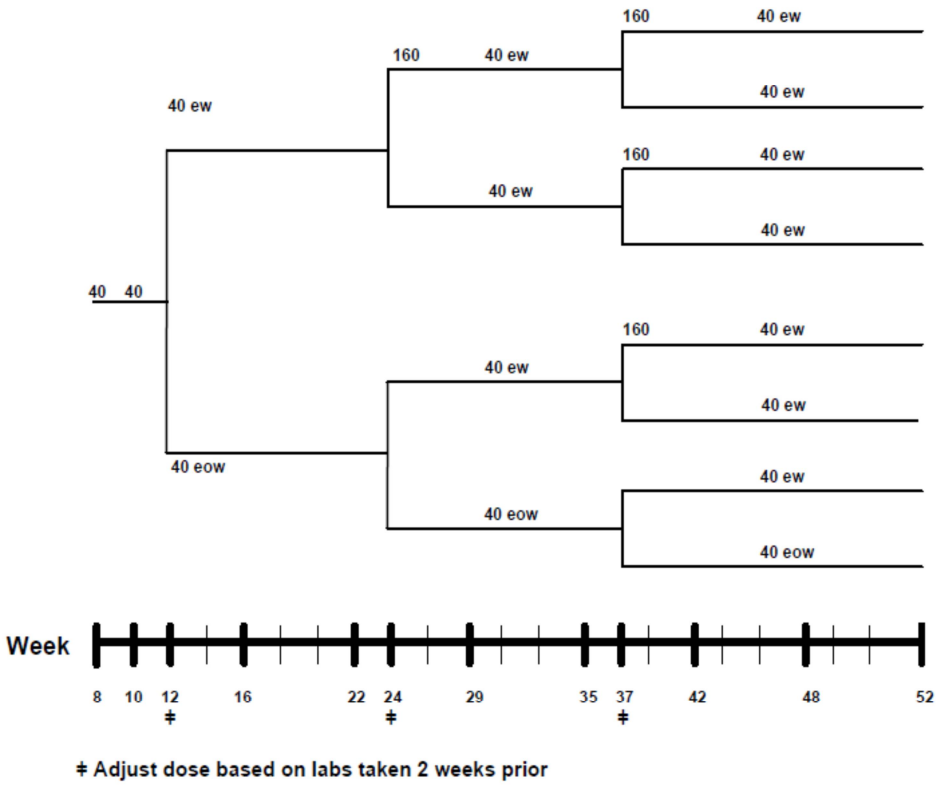
- Adalimumab 40 mg eow
- Adalimumab 40 mg every week (ew)
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory). See Figure 3. (The Japan sub-study does not have a TDM regimen. Subjects will be randomized into Adalimumab 40 mg eow treatment group or Adalimumab 40 mg ew treatment group in a 1:1 ratio.)

At Week 8, subjects will be re-stratified by:

- Treatment regimen in the Induction Study

  and
- Response status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. Among the responders at Week 8, the re-randomization will be further stratified by remission status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) determined at Week 8.

Figure 3. Drug Monitoring (TDM) Regimen



Subjects in the adalimumab 40 mg eow treatment group will continue to receive 40 mg eow until the end of the study. Subjects in the adalimumab 40 mg ew treatment group will start 40 mg ew at Week 8 until the end of the study.

All subjects in the TDM regimen will receive 40 mg eow at Week 8 and Week 10, and may have their adalimumab dose adjusted at Weeks 12, 24, and 37 based on criteria assessing blinded adalimumab serum concentration at the prior visit (Weeks 10, 22, and 35, respectively, Table 1) and rectal bleeding subscore (RBS) at the prior and current visits as follows:

- Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly.

- Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week.

Table 1. TDM Dose Adjustment Criteria

TDM Dose Adjustment Criteria[a]		
Adalimumab Serum Concentration[b]	**Rectal Bleeding Subscore[c]**	**Dose Escalate?[d]**
< 10 µg/mL	Any	Yes
10 µg/mL to 20 µg/mL	< 1	No
10 µg/mL to 20 µg/mL	≥ 1	Yes
> 20 µg/mL	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 SDP.

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

c. The score entries into the subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit, Appendix C.

d. For subjects on 40 mg eow, escalate to 40 mg ew. Subjects on 40 mg ew will receive "reinduction" with a dose of 160 mg at the visit and resume 40 mg ew 1 week later.

Note: There will be no allowance for dose adjustment in the adalimumab eow or ew dosing groups.

Throughout the study, subjects will only be allowed to change the dosage of UC-specific concomitant medications as specified in Section 5.2.3.2.

Subjects will return to the study site at scheduled visits and complete study procedures for each visit as outlined in Section 5.3.1.1. Site staff to ensure all data needed to complete Weeks 12, 24 and 37 is available prior to the subject arriving at the site. Notify the Clinical Research Associate (CRA) should any needed reports be missing. No study drug will be administered or injected at the final visit.

70-Day Follow-Up/Premature Discontinuation

Subjects may discontinue adalimumab treatment at any time during study participation (Section 5.4). Subjects who end study participation early will have a premature discontinuation (PD) Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or

ongoing AEs. The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

5.2 Selection of Study Population

Eight hundred and forty (840) subjects will be enrolled at up to 125 sites in the Main Study.

An additional 100 subjects will be enrolled at approximately 21 sites in Japan as part of a separate Japan sub-study outlined in Appendix K.

Adult male and female subjects who meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of the protocol are eligible to be enrolled into the study.

5.2.1 Inclusion Criteria

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
2. Male or female ≥ 18 and ≤ 75 years of age at the Baseline visit.
3. Subject with a diagnosis of Ulcerative Colitis for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period with exclusion of current infection, dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.
4. Active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) 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 or immunosuppressants as defined below):
    - Subject taking oral corticosteroids, excluding budesonide or beclomethasone:
        - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);

    - For subject 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 subject 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 subject 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 subject 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.
- Subject taking oral beclomethasone:
  - Dose must not exceed 5 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.

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 for their UC from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of UC related symptoms) or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss or response or lack of tolerability will be required, see Section 10.1 and Appendix H.

6. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly 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);
   - A 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.

7. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.
8. Subject has a negative TB Screening Assessment. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline (see Section 5.3.1.1).
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, chest x-ray, and a 12-lead ECG performed during Screening.
10. Subject must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

Rationale for the Inclusion Criteria

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 diagnosis and/or history of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.

4. Received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
7. Positive pregnancy test at Screening (serum) or Baseline (urine).
8. Female who is breast-feeding or considering becoming pregnant during the study.
9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subject on azathioprine, 6-MP, 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.
11. Subject on oral aminosalicylates who:
    - Has not been on stable doses of these medications for at least 14 days prior to Baseline; or
    - Has discontinued use of aminosalicylates within 14 days of Baseline.
12. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subject on oral budesonide > 9 mg/day; or subject on oral beclomethasone > 5 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 of at least 14 days in duration 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 oral 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 of at least 14 days in duration 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 has **not** been a current steroid course of at least 14 days in duration prior to Baseline; or
- Subject taking oral beclomethasone:
  - has **not** been on a stable dose for at least 7 days prior to Baseline; or
    - but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline; or

Has been taking, both oral budesonide (or oral beclomethasone) and oral prednisone (or equivalent) simultaneously.

and/or

Has discontinued use of corticosteroids within 14 days of Baseline.

13. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
14. Positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening Period.
15. Currently receiving total parenteral nutrition (TPN).

16. Subject who received any investigational agent or procedure (including previous fecal microbial transplantation) within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer.

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

18. 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.

19. 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®]) or previous participation in an adalimumab clinical study. Prior exposure to any anti-TNF agent other than infliximab (including but not limited to adalimumab [Humira®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).

20. Subject with known hypersensitivity to the excipients of adalimumab as stated in the prescribing information.

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

22. 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. If the

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

23. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).

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

25. Subjects with a positive result for 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.

26. Chronic recurring infections or active TB.

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

28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

29. 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.

Rationale for the Exclusion Criteria

Criteria	Rationale
1, 2, 3, 5	To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results.
7, 8, 14, 17, 21 – 27, 29	To reduce the risk to subjects or others and/or to exclude underlying conditions that would compromise the subject's safety.
28	To maintain the integrity of other aspects of study conduct, including, subject sampling, treatment procedures, etc.
4, 6, 10 – 13, 15 – 16, 19	To avoid bias for the evaluation of efficacy and safety by concomitant or prior use of other medications or treatments.
9, 18, 20	To exclude subjects who maybe at increased risk for protocol non-adherence or premature discontinue.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Any non-UC related medication or vaccine (including over-the-counter or prescription medicines, vitamins and herbal supplements) that the subject is receiving within 30 days prior to Baseline, is receiving at the time of Enrollment, and/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).

UC-specific medications (including but not limited to oral corticosteroids, oral or rectal aminosalicylates, and immunosuppressant agents) 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 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 (within the past 1 year) or were intolerant (within the past 5 years) to treatment with oral corticosteroids, or immunosuppressants will have the last dosage, dates of administration, maximum dose, and reasons for discontinuation recorded in appropriate eCRF.

If subjects have/had ever been treated with azathioprine, 6-MP, or methotrexate, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will be recorded in appropriated eCRF. For subjects previously treated with infliximab, the infliximab history will be recorded, including the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment. The AbbVie SDP identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapies.

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

5.2.3.2 Concomitant Therapy

Doses of immunosuppressants (including but not limited to azathioprine, 6-MP, and MTX) and aminosalicylates taken at Baseline will be continued. Doses must remain stable from Baseline throughout the duration of the study. Doses may be decreased or

terminated in the event of moderate-to-severe treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) in the opinion of the investigator.

Doses of oral corticosteroids taken at Baseline (as outlined in inclusion criterion 4 in Section 5.2.1) will be continued. Subjects may not be on both oral budesonide (or oral beclomethasone) and oral prednisone (or equivalent) simultaneously. Subjects may not 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 oral corticosteroid therapy at Baseline will have their corticosteroid therapy tapered according to the proposed tapering schedule specified 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.

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

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.

Subjects in whom the following UC-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.

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

Changes in all concomitant medications will be assessed at each study visit from Baseline (Week 0) through Week 52/PD Visits. Any changes will be documented in the source documents and captured on the appropriate eCRF page.

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®);
  - Infliximab (Remicade®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Efalizumab (Raptiva®);
  - Golimumab (Simponi®);
  - Certolizumab pegol (Cimzia®);
  - Ustekinumab (Stelara®);

  - Belimumab (Benlysta®);
  - Vedolizumab (Entyvio®).
- Live vaccines (during the study and for 70 days after the last dose of study drug).
- Cyclosporine, tacrolimus, or mycophenolate mofetil (within 30 days prior to Baseline and during the study).
- Tofacitinib (Xeljanz®).
- Recreational or medical marijuana use 14 days 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 7 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 or investigational procedures (including previous fecal microbial transplantation) are prohibited within 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline and during the study.

The AbbVie SDP 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 into the study.

Table 2. Study Activities

Activity	Screening Period (21 days)	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Informed Consent	X																		
Inclusion/Exclusion	X	X[b]																	
Medical/Surgical History	X	X[b]																	
Previous and Concomitant Medication	X	X[b]	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	X	
Schedule Endoscopy	X				X											X			
Endoscopy/Biopsy[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/Hematology[i]	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	
Urinalysis[i,j]	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	

Table 2. Study Activities (Continued)

Activity	Screening Period	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Pregnancy Test[k]	X	X															X		
Hepatitis B Screen, HIV[l]	X																		
hs-CRP	X	X				X		X	X		X	X		X	X		X	X	
C. difficile Toxin	X																		
Provide Stool Kit [m]	X				X		X	X		X			X			X			
Stool Sample (Fecal Calprotectin)[m]	X					X		X	X		X			X			X		
Stool Sample (Microbiota Metagenomic Analysis)[m]	X					X			X		X						X		
Bristol Stool Chart [m]	X					X			X		X						X		
Antinuclear antibody (ANA)/ Anti-Double-Stranded DNA (anti-dsDNA)[n]	X																		
Human Antichimeric Antibodies (HACA)/ Infliximab Concentrations		X																	

Table 2. Study Activities (Continued)

Activity	Screening Period	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Adalimumab Concentration[o]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AAA Concentration[o]		X			X	X		X			X			X			X	X	
Pharmacogenetic (optional)[p]		X															X		
Serologic Markers/mRNA		X		X	X	X					X						X		
Inflammatory Bowel Disease Questionnaire (IBDQ)		X		X	X	X		X			X			X			X		
Partial Mayo Score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mayo Score		X				X											X		
SF-36		X				X											X		
Work Productivity and Impairment Questionnaire (WPAI)		X				X											X		

Table 2. Study Activities (Continued)

Activity	Screening Period	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Start Corticosteroid Taper[q]					X														
Monitor Adverse Events[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Daily Diary[s]	X																		
Daily Diary[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject Trained on Self-Administration of Injections		X																	
Study Drug Dispensing/ Administration[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

a. The 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.

Table 2. Study Activities (Continued)

d. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy for histologic assessment during Screening, at Week 8 and at Week 52/PD (for subjects who remain in the study through at least Week 24). A full colonoscopy will be performed at Screening unless the subject underwent a full colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis and extent of disease and no current evidence of dysplasia and colon cancer). In this case, the screening endoscopy may be either a full colonoscopy or a flexible sigmoidoscopy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, 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 colon must be performed during the Screening endoscopy and evaluated by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to rule out current dysplasia and colon cancer may be taken during any study endoscopy per the Investigator's discretion and evaluated by the local pathologist. The Week 8 and Week 52/PD endoscopies may be either full colonoscopies or flexible sigmoidoscopies. During all endoscopies, 2 biopsies for histologic evaluation by a central laboratory will be taken from each observed colonic segment (see Section 5.3.1.1 for details about biopsy sampling).

e. Physical examinations performed at Screening, Week 8 and Week 52/PD Visits are full physical examinations which must include an assessment of extra-intestinal manifestations (EIMs). Physical exams performed at all other visits are symptom-based.

f. Subjects with negative latent TB test(s) (In cases where a subject received both a PPD test and IGRA, both must be negative) within 90 days of Screening will not require a repeat latent TB 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 will not require a repeat chest x-ray, if documentation is available.

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

i. Laboratory 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. A serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy test will be performed at Baseline Visit, and at the Week 52/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 Section 5.3.1.1 in the Hepatitis B testing section 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.

Table 2. Study Activities (Continued)

m. 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 the site. 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. Remaining sample will be stored for potential research testing.

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

o. Blood samples for the measurement of adalimumab, AAA concentrations, serologic markers and mRNA will be collected prior to dosing. **All adalimumab samples should be shipped the same day they are collected at Weeks 10, 22 and 35 to ensure adequate processing time to determine blinded serum concentration levels needed for dosing adjustments, where applicable, at Weeks 12, 24 and 37. Note:** 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.

p. Verify subject has signed consent for optional pharmacogenetic sample prior to the sample drawn. If the sample is not collected at Baseline, preferably it should be collected at the next study visit.

q. Subjects will begin the 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 Serious Adverse Events (SAEs) begins the day the subject signs the informed consent.

s. Subjects will be dispensed the subject 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, including during hospitalizations whenever possible. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD visit.

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

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

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.

5.3.1.1 Study Procedures

The study procedures outlined in Table 2 are discussed in detail in this section, with the exception of drug and HACA/Infliximab concentration measurements, antibody measurements, and serologic and mRNA biomarkers (discussed in Section 5.3.2, Section 5.3.1.3, and Section 5.3.5.2), 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 (including Medication) and Surgical History

A complete medical and surgical history (which includes UC-onset date), 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.

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

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

Vital Signs

Vital sign determinations of sitting blood pressure (diastolic and systolic), pulse rate, respiratory rate, body temperature, and body weight will be obtained at each visit prior to blood draws. Weight measurements of subjects (with clothes on) should be obtained at each visit using the same measuring instrument. Height will be measured at the Screening Visit only. All measurements will be recorded in metric units when applicable.

Endoscopy

All endoscopies should be recorded in a video format at the time points noted in Table 2. Endoscopies will be reviewed by a primary central reviewer who is blinded to the subject's clinical data, the site's endoscopy assessment and the subject's therapy. If, in the assessment of the endoscopist, the Screening endoscopy does not indicate an endoscopy subscore of 2 or 3 per eligibility requirements, the subject should be screen-failed and the video should not be sent for central review. The endoscopy during the Screening period, at Week 8 and Week 52/PD Visit (for subjects who remain in the study through at least Week 24) will be used for calculation of the endoscopy subscore of the Mayo Score, refer to Appendix C. The endoscopy subscore will be documented by the endoscopist at the site and maintained in the subject's source documents. The endoscopist will also document the presence or absence of friability in the subject's source documents and eCRF.

Screening endoscopy: A full colonoscopy will be performed at Screening unless the subject underwent a full colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis and extent of disease and no evidence of current dysplasia and colon cancer). In this case, the screening endoscopy may be either a full colonoscopy or a flexible sigmoidoscopy.

The endoscopy subscore result from the central reviewer will be entered into the eCRF by the site and used to evaluate the eligibility of a subject at Baseline for the study. A second central read (adjudication) of the screening endoscopy will be required if the subject's eligibility for the study is discrepant between the site and central reader. For instance, if a site endoscopist scores the endoscopy subscore of 2 and the central reader provides a score of 1, the subject's ability to be enrolled would be in question and that would lead to an adjudication using a second central reader as outlined in the endoscopy central reader manual. The adjudicator will perform an independent review with read-only access to both site and central assessments (blinded to the source of assessments). The adjudicator will not provide an assessment but will select the assessment with whom he/she agrees. The adjudicator's assessment will be considered final.

Week 8 and Week 52/PD endoscopy: The Week 8 and Week 52/PD endoscopies may be either full colonoscopies or flexible sigmoidoscopies. The site's endoscopist scoring will be entered into the eCRF by the site and used for the Mayo score calculation for the purposes of re-randomization. The central reader's assessment will be used for the Mayo scores used in all efficacy endpoint assessments.

Only endoscopists designated to take part in the study will perform the endoscopies.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of UC, 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 colon must be performed during the Screening

endoscopy and read by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to rule out dysplasia and colon cancer may be taken during any study endoscopy per the Investigator's discretion and evaluated by the local pathologist.

The signed pathology reports confirming the diagnosis and when appropriate, ruling out current dysplasia/malignancy will be monitored by the responsible CRA and kept with the subject's source documents onsite. Subjects will not be enrolled if colon dysplasia or colon cancer is discovered at the Screening endoscopy. If a diagnosis of colon dysplasia or colon cancer 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.

Additional tissue biopsy sample(s) will be collected from each observed bowel segment (rectum, sigmoid, descending colon, transverse colon, ascending colon/cecum) and stored for histologic analysis by a central laboratory, as described below.

Up to 10 biopsy specimens per subject should be obtained at each endoscopy for histologic assessment. Two (2) biopsies should be taken from each observed segment of the colon (rectum, sigmoid, descending colon, transverse colon, ascending colon/cecum). One biopsy should be taken from the area of most inflammation (if the area is ulcerated, the sample should be obtained from the edge of the ulcer). The second biopsy should be taken from an area that is representative of the general degree of mucosal inflammation present in that segment.

For all histology biopsies, the location of the biopsy specimen (distance from the anal margin) should be recorded.

In the absence of any visible lesions or areas of general inflammation characteristic of ulcerative colitis, one biopsy specimen should be collected from normal mucosa in the same segments as noted above.

Biopsy Sample Collection, Storage and Shipping:

Biopsies performed to confirm the diagnosis of UC or to rule out current dysplasia/malignancy should be processed and read locally per site standards.

Up to 10 biopsy specimens per subject should be obtained by endoscopy for histologic assessment at Screening, Week 8, and Week 52/PD. Using routine forceps for tissue collection, obtain the required number of biopsy specimens from each of the identified regions and process the specimens following the instructions in the Investigator Manual provided by the laboratory.

Tissue Analysis

The following analyses will be sent to the central laboratory and performed on formalin-fixed samples:

1. Qualitative ulcerative colitis histological assessment for the colon using a histologic scoring system.
2. These samples may not be read in real time, however if unexpected findings, such as dysplasia, are noted on the histology biopsies, the central laboratory will contact the Investigator to inform him/her about the unexpected finding. Subjects who are found to have dysplasia on the submitted biopsy will be terminated from the trial at the time the dysplasia is discovered. Unexpected findings should be recorded as an adverse event.
3. Any remaining tissue (per local requirements) 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, and/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).

Physical Examination

A physical exam will be performed at the designated study visits as outlined in Table 2. Physical examinations performed at Screening, Week 8 and Week 52/PD Visits are full physical examinations and must include an assessment of extra-intestinal manifestations (EIMs). Physical exams performed at all other visits are symptom-based.

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

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 chest x-ray 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 chest x-ray 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 test 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 with another blood sample or perform a PPD

test. If the second IGRA test is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis.

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 in 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 residence 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.

Chest X-Ray

All subjects will undergo a standard chest x-ray (PA **and** lateral views) at the Screening Visit to rule out the presence of TB or other clinically relevant findings. The chest x-ray 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).

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.

Subjects can have a repeat chest x-ray at any time during the study as warranted based on the opinion of the Investigator.

12-Lead ECG

A resting 12-lead ECG will be performed at the designated study visits in Table 2. 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.

Laboratory Assessments

Samples obtained for the laboratory tests will be collected as indicated in Table 2. Blood draws should be performed after efficacy assessments and vital sign determinations are

made. Additional laboratory tests may be obtained when clinically warranted. Should a laboratory test value be outside the reference range and be considered by the Investigator to be clinically significant, the test should be repeated to verify the result. All laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

The Central Laboratory chosen for the study will process the samples and provide results for the clinical laboratory tests indicated in Table 3.

The last clinical laboratory test value obtained prior to randomization will serve as the baseline laboratory test values. Laboratory abnormalities are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

The laboratory results will be sent from the central laboratory to the investigative site where they will be reviewed, signed and dated by the Investigator. The central laboratory will provide instructions regarding the collection, processing, and shipping of 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 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 will not be made aware of any positive result.

Table 3. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis[a]
Hematocrit Hemoglobin Red Blood Cell count White Blood Cell 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
Additional Blood Samples Collected		**Stool Samples Collected**
Pharmacokinetic hs-CRP Pharmacogenetic (optional) mRNA HACA Infliximab Serologic Biomarkers ANA anti-dsDNA – *if ANA positive* β-HCG HBV HIV, if applicable (testing to be conducted at local lab)		*C. Difficile* toxin Fecal calprotectin Microbiota metagenomic analyses

a. 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 2. 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.

Pregnancy Tests

A serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy tests will be performed locally by designated study personnel at the Baseline Visit, and at the Week 52/PD for all women of childbearing potential. The frequency can be increased up to every visit as per local regulations.

If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

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.

hs-CRP

Blood samples for hs-CRP will be obtained as indicated in Table 2.

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

Antinuclear Antibody and Anti-Double-Stranded DNA

ANA will be performed and if positive, anti-dsDNA will be performed as indicated in Table 2.

Pharmacogenetic Sample

Samples will be obtained for pharmacogenetic analysis at the designated study visits in Table 2 These analyses are described in more detail in Section 5.3.1.2.

Other Laboratory Assessments

Stool Sample (Fecal Calprotectin, *C. Difficile*, and Metagenomic Analyses)

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, fecal calprotectin and microbiota metagenomic analyses. Subjects will be sent home with a stool sample supply kit as indicated in Table 2 if a sample cannot be obtained during the site visit. The site will give instructions to the subjects with the 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. All microbiota metagenomic analyses stool samples should be scored using the Bristol stool chart (Appendix I) by site staff. A central laboratory(s) will be utilized to process these laboratory samples. The samples must be shipped to the central laboratory using dry ice. Additional information is available in the Investigator Manual provided by the central laboratory. Subjects can Re-screen if they have a positive *C. difficile* at Screening, are treated appropriately, and have a negative *C. difficile* upon completion of treatment.

Fecal calprotectin and microbiota metagenomic analysis will be performed for all subjects as indicated in Table 2. Fecal calprotectin and microbiota metagenomic results will remain blinded to the Investigator, study site personnel and the subject throughout the study.

Any remaining stool (per local requirements) 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, and/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.

Outcome Assessments

IBDQ

IBDQ will be completed at the time points indicated in Table 2 (Appendix F).

Mayo Score/Partial Mayo Score

Data from the patient diaries will be collected so Mayo score/Partial Mayo Score may be calculated at the time points indicated in Table 2.

Whenever possible, the same physician (investigator or subinvestigator) should determine the Physician's Global Assessment (PGA) subscore for an individual subject through the duration for the study. The directions for capturing the stool frequency subscore, rectal bleeding subscore, and PGA subscores of the Mayo score are described in Appendix C.

SF-36v2™ Health Status Survey

The SF-36v2™ form contains 36 total questions targeting a subject's functional health and well-being, as well as his/her psychometric physical and mental health. Subjects will complete the SF-36 at the visits indicated in Table 2 (Appendix G).

Work Productivity and Impairment Questionnaire (WPAI)

Subjects will complete the WPAI Questionnaire at the time-points indicated in Table 2. The data in the subject-completed questionnaire will be transferred to the appropriate eCRF by the site personnel at each study visit (Appendix D).

Corticosteroid Therapy

At and after Week 4, subjects who are on oral prednisone (or equivalent) or budesonide or beclomethasone will initiate a taper of their corticosteroid dose. 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 tapering schedule is shown below.

	Dose	Rate
Prednisone (or equivalent)	> 10 mg/day ≤ 10 mg/day	5 mg/day/week 2.5 mg/day/week
Beclomethasone	5 mg/day	Discontinue

	Dose	Rate
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 (or oral beclomethasone) 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 subject 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 E.

Adalimumab injections occurring during study visits will be performed at the visit by the subject or his/her 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 first four doses of study drug will be administered on site the same day at the Baseline Visit and Week 1 Visit. On Week 2, 24 and 37 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. 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.

A ± 3-day dosing window is allowable for scheduled study dosing dates. For subjects who deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the ± 3-day dosing window, please contact the Monitor 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 medication should be discontinued immediately and appropriate therapy initiated. When dosing at home subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction. If subjects are unable to reach his/her 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.

5.3.1.2 Blood Sample for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected per Table 2 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.

5.3.1.3 Blood Samples for Biomarker Analysis

Collection of Samples for Serologic Markers

Two 5 mL blood samples for serologic markers analysis (refer to Section 5.3.5.2) will be collected at the time points indicated in Table 2. Please refer to the laboratory manual for instructions.

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.

Collection of Samples for mRNA Assays

Two 2.5 mL blood samples for mRNA (refer to Section 5.3.5.2) will be collected at the time points indicated in Table 2. Please refer to the laboratory manual for 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 mRNA samples to AbbVie or specified lab for testing.

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 2.

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 22 samples (not including unscheduled visit sample collections) are planned to be collected per subject for adalimumab (15 samples) and AAA (7 samples) assays. The total number of samples planned (not including unscheduled visit sample collections) will not exceed 12,600 (15 samples × 840 subjects) for the adalimumab assay and 5,880 (7 samples × 840 subjects) for the AAA assay for the main study.

Collection of Samples for Infliximab and HACA Assays

Blood samples for infliximab and HACA assay will be collected at Week 0 (Baseline) by venipuncture into appropriately labeled 4-mL evacuated serum collection tube without gel separator at Baseline. 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 1,680 (2 samples × 840 subjects) for the main study.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab, AAA, infliximab and HACA assays will be labeled with the type of sample, the protocol number, the subject number, the week and the 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.

IMPORTANT: All adalimumab samples should be shipped the same day they are collected at Weeks 10, 22 and 35 to ensure adequate processing time to determine blinded serum concentration levels needed for dosing adjustments, where applicable at Weeks, 12, 24, and 37.

5.3.2.3 Disposition of Samples

Frozen 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 CRA. An inventory of the samples will be included in the package for shipment. Arrangements will be made with the central lab for the transfer of samples.

5.3.2.4 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Primary Variables

The primary efficacy variable for the Induction Study is the proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy variable for the Maintenance Study is the proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

5.3.3.2 Secondary Variables

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Induction Study are:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.
2. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.

3. Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 8.
4. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.
5. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Maintenance Study are:

1. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
2. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
4. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.
5. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
7. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
8. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 52.

9. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
10. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
11. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
12. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

The steroid-free endpoints require subjects to have discontinued steroids for at least 90 days. While steroid therapy is associated with significant toxicity, durable steroid-free status may be more clinically meaningful than discontinuation evaluated simply at a single point in time. A position paper on endpoints in ulcerative colitis trials suggested that the minimal clinically significant corticosteroid-free duration is unclear, but the authors suggested that 3 months or longer represented a clinically meaningful endpoint in therapeutic trials.[14] The duration of steroid-free status should also be considered within the context of the duration of the clinical study, the maximum allowed steroid dose at Baseline, and the tapering schedule. Based on these factors, 90 days was felt to be clinically meaningful and therefore this duration was selected for the ranked secondary endpoints that evaluate steroid-free status in this study.

5.3.3.3 Additional Variables

Additional pre-specified endpoints in the Induction Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Induction Study.
- All-cause and UC-related hospitalization and surgery rates during Weeks 0 – 8.
- Change from Baseline in histologic score at Week 8.

- Proportion of subjects achieving clinical remission per Adapted Mayo Score (defined as stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1) at Week 8.
- Proportion of subjects achieving Full Mayo score excluding the PGA subscore, ≤ 2 with no subscore > 1 at Week 8.
- Relationship between histologic subscores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 8.
- Relationship between histologic scores and endoscopic subscore of 0 as Week 8.

Additional pre-specified endpoints in the Maintenance Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Maintenance Study by Week 8 response status.
- Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic improvement at Week 52.
- All cause and UC-related hospitalization and surgery rates during Weeks 8 – 52.
- Change from Baseline in histologic score at Week 52.
- Proportion of Week 8 responders per Adapted Mayo score (defined as decrease from Baseline in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1) achieving clinical remission per Adapted Mayo scores at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) achieving Full Mayo Score, excluding the PGA subscore ≤ 2 with no subscore > 1 at Week 52.
- Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 52.

- Relationship between histologic scores and endoscopic subscore of 0 at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.

The following additional pre-specified endpoints will also be analyzed in both the Induction Study and the Maintenance Study.

- Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.
- Proportion of subjects who are taking corticosteroids at Baseline and are steroid free over time.
- Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.
- Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score ≤ 2 with no subscore > 1) score over time.
- Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of ≥ 2 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) over time.
- Change from Baseline in hs-CRP over time.
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in IBDQ score over time.
- Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.

- Change from Baseline in SF-36 score over time.
- Change from Baseline in fecal calprotectin over time.
- Time to achievement of remission (per Partial Mayo score)
- Time to achievement of response (per Partial Mayo score)
- Time to loss of response and factors associated with loss of response.
- Change in presence of extraintestinal manifestations over time.

5.3.3.4 Safety Variables

Safety will be assessed by adverse events, physical examination, vital signs and laboratory data during the entire study.

5.3.4 Pharmacokinetic Variables

Serum concentrations of adalimumab at each scheduled sampling time will be summarized and stratified by treatment regimen. The number and percentage of subjects who develop AAA will be determined. The adalimumab concentration data may be analyzed using a nonlinear mixed effects model (population PK analysis). The relationship of response (primary efficacy variables and other responses of interest) with study drug exposure will be explored.

5.3.5 Pharmacogenetic and Serologic Variables

5.3.5.1 Pharmacogenetic Variables

Samples may be sequenced and data analyzed for DNA sequences contributing to the disease or to the 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.

5.3.5.2 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, adverse events, 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.

5.4 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 drug 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 medication.
- 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 PD 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 PD. 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

Double-Blind Induction Study

At Baseline (Week 0), subjects will be randomized 3:2 to one of two double-blind adalimumab induction dosing regimens.

Subjects assigned to the standard induction dosing regimen will receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and matching placebo (4 syringes) at Week 1. At Week 2, subjects will receive 80 mg (2 syringes) and matching placebo (2 syringes) At Week 3, subjects will receive matching placebo (4 syringes) and at Weeks 4 and 6, subjects will receive a dosing regimen of 40 mg (1 syringe).

Subjects assigned to the higher induction dosing regimen will receive 160 mg (4 syringes) at Weeks 0, 1, 2, and 3 followed by 40 mg (1 syringe) at Weeks 4 and 6.

Double-Blind Maintenance Study

At Week 8, subjects will be re-randomized to receive 1 of 3 double-blind adalimumab treatment maintenance regimens in a 2:2:1 ratio.

Subjects assigned to the adalimumab 40 mg eow regimen will receive 40 mg (1 syringe) at Weeks 8, 10, 12, 14, 16, 18, 20, 22, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and 50. Subjects will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24. At Week 37, subjects will receive matching placebo (4 syringes). Matching Placebo (1 syringe) will be administered at Weeks 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects assigned to the adalimumab 40 mg ew regimen will receive 40 mg (1 syringe) at Weeks 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. Subjects will receive 40 mg (1 syringe) and placebo (3 syringes) at Weeks 24 and 37. No dose will be administered at Week 52/Premature Discontinuation.

Subjects assigned to the TDM regimen will receive adalimumab 40 mg eow (1 syringe) at Week 8 and Week 10. Matching placebo (1 syringe) will be administered at Weeks 9 and 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria in Table 1.

Subjects who don't dose escalate at Week 12 will receive 40 mg eow (1 syringe) at Weeks 12, 14, 16, 18, 20, and 22 and placebo (1 syringe) at Weeks 13, 15, 17, 19, 21 and 23. Subjects who escalate at Week 12 will receive 40 mg ew (1 syringe) at Weeks 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 and 23.

Subjects who don't dose escalate at Week 24 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg eow (1 syringe) at Weeks 26, 28, 30, 32, 34, and 36 and placebo (1 syringe) at Weeks 25, 27, 29, 31, 33 and 35. Subjects who escalate at Week 24 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36.

Subjects who don't dose escalate at Week 24 and were receiving adalimumab 40 mg ew will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg

ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36. Subjects who escalate at Week 24 and were receiving adalimumab 40 mg ew will receive 160 mg (4 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36.

Subjects who don't dose escalate at Week 37 and were receiving adalimumab 40 mg eow will receive placebo (4 syringes) at Week 37, followed by 40 mg eow (1 syringe) at Weeks 38, 40, 42, 44, 46, 48, and 50 and placebo (1 syringe) at Weeks 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects who escalate at Week 37 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects who don't dose escalate at Week 37 and were receiving adalimumab 40 mg ew will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects who escalate at Week 37 and were receiving adalimumab 40 mg ew will receive 160 mg (4 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 4.

Table 4. Study Drugs

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Pre-filled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie
Placebo	Parenteral	Pre-filled syringe	0.8 mL 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 medication at all times, and should never be removed for any reason.

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

5.5.2.2 Storage and Disposition of Study Drug(s)

Adalimumab/placebo pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study medication drug ***must not be frozen*** at any time. A storage

temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded on a temperature log to record proper function. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study medication should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) or other 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 Inc.

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 Regimens

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 Induction Study. Subjects who enter the Induction Study will be randomized at Week 0 in a 3:2 ratio into the criteria-driven regimens using the IRT, which will assign a randomization number according to the randomization scheme, generated by AbbVie before the start of the study. The randomization will be stratified by previous infliximab use and Baseline corticosteroid use. The criteria-driven regimen assignment will be maintained by the IRT. Subjects will be referred to by the subject number assigned at Screening.

Subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Study at the conclusion of the Week 8 Visit to one of three treatment regimens in a 2:2:1 ratio. Subjects will be re-stratified by: induction treatment regimen and response status (per Full Mayo Score) at Week 8. Among Week 8 responders, the randomization will be further stratified by remission status (per Full Mayo Score) at Week 8.

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 IRT will be provided to each site. Study drug will be dispensed/administered at the study visits summarized in Table 2.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1. If a subject should forget to administer the injection of study medication on his/her regularly scheduled dosing date, he or she should take the forgotten injection as soon as they remember the dose was missed up to the day of his/her next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all home 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 his/her 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 the AbbVie Drug Supply Management Team) the Investigator, study site personnel and the subject will remain blinded to each subject's treatment throughout the blinded period of the study. The IRT will provide access to blinded subject treatment information in the case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie SDP

(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 and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The subject or his/her 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 administered at home. 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 (or information is not available electronically), 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 or available electronically 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. Each subject will be given his/her 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 medication accountability via study medication logs, source documents, subject diary, 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 Regimens

Study M14-033 is a global, randomized, multicenter study of standard versus higher adalimumab dosing regimens for induction and maintenance therapy in subjects with moderately to severely active UC. No placebo regimen is planned due to documented efficacy of adalimumab in UC and the purpose of this study is to investigate whether greater efficacy is achieved with the higher dose than with the standard dose, and to compare safety outcomes. Additionally, since subjects will have evidence of endoscopic damage confirmed by a central reader and clinical symptoms consistent with moderately

to severely active UC, it would be not medically acceptable to deny those subjects effective treatment and it would be difficult to enroll subjects in the trial when the drug is available to be prescribed for UC.

The study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active UC.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The clinical efficacy measurement used in this study (Mayo Score) has been used in multiple pivotal clinical trials in assessing disease activity in subjects with UC.[12,13] All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Subjects with moderately to severely active UC who meet all inclusion criteria and none of the exclusion criteria are eligible for this study. The specific subject population chosen was based on unmet medical needs of currently available medical therapies as well as previous anti-TNF studies that demonstrated effectiveness in UC.[13]

5.6.4 Selection of Doses in the Study

Dose regimens and numbers of subjects were determined based on efficacy and safety data from the adult UC population from Study M06-827, PK/pharmacodynamic modeling using PK and efficacy data from Study M06-827 and observed safety data from high dose adalimumab IV studies in rheumatoid arthritis.

Induction Dose Selection

The use of higher induction doses than 160/80 mg in adult subjects with moderately to severely active UC is supported by exposure-efficacy analyses from Study M06-827. At Week 8 of Study M06-827, serum trough adalimumab concentrations ranged from 0 to 22.8 µg/mL following dosing with 160/80 mg at Weeks 0 and 2 and 40 mg at Weeks 4

and 6. The highest rate of remission (25.4%) was observed in subjects in the highest concentration quartile, in which most observed concentrations ranged from 12 to 16 µg/mL. The higher induction regimen selected for testing represents an approximate doubling in adalimumab exposure over the first 8 weeks compared to the standard dose, and is expected to achieve a higher rate of remission at Week 8 compared to the standard approved induction dose regimen.

Maintenance Dose Selection

In order to test the efficacy and safety of a wide range of adalimumab exposure during maintenance therapy for UC three dosing strategies will be tested. Two fixed doses, 40 mg eow (the currently approved maintenance dose) and 40 mg weekly will be tested. An exploratory regimen evaluating a TDM strategy will also be evaluated. The goal of the TDM maintenance dosing regimen is to analyze the feasibility, efficacy, and safety of aiming for serum adalimumab levels within a targeted concentration range for making decisions regarding dosing.

The targeted concentration range selected for the TDM dosing regimen was based on serum concentrations observed during Study M06-827 and the mean serum concentrations observed in subjects who achieved remission during this study. During maintenance therapy in Study M06-827, concentrations with maintenance dosing ranged from 0 to 39.3 µg/mL with eow dosing and 0 to 38.0 µg/mL with 40 mg weekly dosing. The lower bound of the targeted concentration range (10 µg/mL) for the TDM regimen is based on serum concentrations in Week 52 remitters in Study M06-827. In those subjects, the median concentrations observed over time were 11.4, 10.6, and 10.8 µg/mL, for Weeks 8, 32, and 52, respectively.

Use of this concentration minimum threshold to trigger dose escalation is expected to lead to the majority of subjects achieving concentrations greater than 10 µg/mL. Since serum adalimumab concentrations roughly double with a doubling of dose, an upper bound of 20 µg/mL is expected to achieve maximal trough concentrations in the range of highest trough concentrations observed in Study M06-827. Based on observed adalimumab

pharmacokinetics in Study M06-827, it is expected that approximately 60% of subjects in the TDM dosing regimen will escalate to 40 mg weekly dosing, and approximately 15% will receive re-induction thereafter using this concentration range and the RBS criteria described in Table 1 as a guide to adjust dosing.

6.0 Complaints

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

The investigational product in this trial contains both:

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1.1 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, (refer Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be adverse events.

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

6.1.1.2 Serious Adverse Events

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

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

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

6.1.2 Adverse Event Severity

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

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

6.1.3 Relationship to Study Drug

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

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

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

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

6.1.4 Adverse Event Collection Period

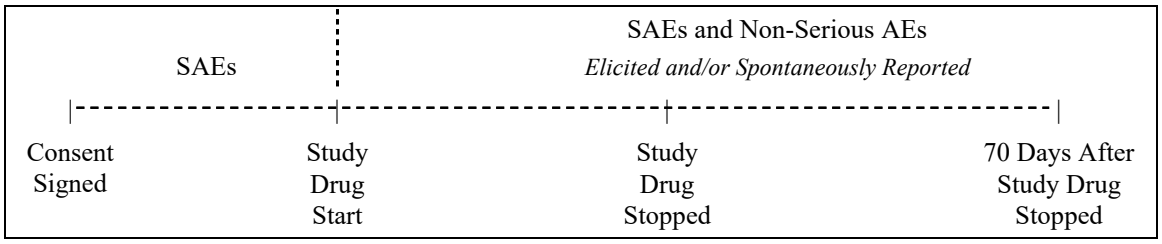
All adverse events reported from the time of study drug administration until 70 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the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

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

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 4). Thus, all SAEs and non-serious AEs, as defined by AbbVie, as well as the medication for AEs/SAEs, reported during the 70-day follow-up phone call must be captured in the clinical database via the eCRF and also recorded in source documentation (Appendix J). 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 4.

Figure 4. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 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 SAE or non-serious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® system or if RAVE® is not operable, should be documented on the SAE Non-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]

Office: [redacted]
Email: [redacted]

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

Primary Study Designated Physician

[redacted] MD
[redacted]
Immunology Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

Contact Information:
Phone: [redacted]
Mobile:
Fax:
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 Humira 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).

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

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

6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (see Section 6.1.1 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

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

6.2 Product Complaint

6.2.1 Definition

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

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling

discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

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

is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying IEC/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned Clinical Monitor or the following AbbVie Clinical Monitor(s):

Primary Contact:

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

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

Alternate Contact:

[redacted] MD
Immunology Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

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

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis. The following statistical analysis plan is for subjects recruited in the main study. A separate statistical analysis plan will be provided for subjects recruited in the Japan sub-study and for all the subjects recruited in the main study and the Japan sub-study (See Appendix K).

Complete, specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP) for the main study and the Japan sub-study. The SAPs will be finalized prior to the database lock.

8.1.1 Analysis Population

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

Intent-to-Treat (ITT1) population includes all subjects who were randomized at Baseline. ITT1 subjects will be analyzed as randomized. ITT1 is the primary population for the efficacy analysis at Week 8 during the Induction Study.

Intent-to-Treat maintenance (ITT2) population includes all subjects who are re-randomized at Week 8 to the Maintenance Study. ITT2 subjects will be analyzed as randomized. ITT2 is the primary population for the efficacy analysis at Week 52 during 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 Variables

The primary efficacy endpoint for the Induction Study is:

Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

The primary analysis of the Induction Study will compare the subjects in the higher adalimumab induction regimen versus the standard adalimumab induction regimen in the ITT1 analysis set. The difference between the treatment regimens in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use at Baseline. A CMH based two sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 8 endpoint. Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non responders.

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as

Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint for the Induction Study.

The primary analysis of the Maintenance Study will compare the Week 8 responders (per Full Mayo Score) in the eow regimen versus the subjects in the ew regimen in the ITT2 analysis set. The difference between the treatment regimens in the proportion of subjects achieving clinical remission at Week 52 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for Induction treatment regimen and the remitter status (per Full Mayo Score) at Week 8. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 52 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 52 endpoint. Subjects with missing Mayo score data for Week 52 will also be classified as Week 52 non-responders.

The TDM regimen will be used for exploratory analyses.

8.1.4.2 Secondary Efficacy Variables

The 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 an alpha level of 0.050 (two-sided) in ranked endpoint order until the significant level exceeds 0.05. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables. For the Induction Study endpoints, the difference between the higher adalimumab induction regimen versus the standard adalimumab induction regimen will be assessed using ITT1 analysis set. For the Maintenance Study endpoints, the difference between the eow dosing regimen versus the ew doing regimen will be assessed using Intent-to-Treat maintenance (ITT2) analysis set where Week 8 responder/remitter status will be determined based on the Full Mayo score using endoscopy subscore from the central reader. Categorical data will be described by frequency and percentage; continuous data will be described by mean, standard deviation,

minimum, median, and maximum. In general, the secondary endpoints at Week 8 that are of the binary type will be analyzed using a two-sided CMH test adjusted for previous infliximab use and Baseline corticosteroid use in the ITT1 analysis set, and the secondary endpoints at Week 52 that are of the binary type will be analyzed using a two-sided CMH test adjusted for induction treatment regimen, and remitter status (per Full Mayo score) at Week 8 (where applicable) in the ITT2 analysis set. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. Continuous secondary efficacy variables will be analyzed using Analysis of Covariance (ANCOVA) with factor for treatment regimen, stratification variables and Baseline values. NRI for missing data will be used for categorical endpoints. Procedures for handling missing data for continuous endpoints will be described in the Statistical Analysis Plan.

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 Studies using the safety analysis set which includes all subjects who receive at least one dose of study medication in each Study respectively. Treatment-emergent AEs, will be tabulated by MedDRA preferred term by treatment group for the Induction Study and the Maintenance Study, and for any adalimumab over the entire study. Mean changes in vital signs, physical examination results, ECGs, and clinical laboratory data values will be analyzed.

8.1.6 Other Statistical Analyses of Efficacy

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

- Sex (male, female)
- Age (≤ median, > median)
- Race (white, non-white)
- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- Baseline Mayo Score (≤ 9, > 9)

- Baseline Mayo Score (≤ median, > median)
- Prior exposure to anti-TNF (yes, no)
- Baseline weight (≤ median, > median)
- Presence of pancolitis at Baseline (yes, no)
- Disease duration at Baseline (≤ median, > median)
- Baseline hs-CRP (≤ 5 mg/L and > 5 mg/L)
- Baseline hs-CRP (≤ median, > median)
- Baseline Albumin (≤ median, > median)
- Region (US versus non-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 8 may be performed after the last subject in ITT1 population completes the 8-week double-blind Induction Study of the main 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 primary efficacy endpoint of the Induction Study, no adjustment of alpha-level is necessary.

8.1.8 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized by treatment regimen 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

When Protocol M14-033 was initially designed, AbbVie used an assumption regarding induction response rate in order to calculate the expected number of Week 8 responders that would comprise the analysis set used to compare the Week 52 remission rates in the adalimumab 40 mg every other week and 40 mg weekly groups. AbbVie assumed that the overall response rate (per Full Mayo Score) at Week 8 would be 60%, which would provide 315 Week 8 responders for the analysis of Week 52 remission (126 in the every other week dosing group, 126 in the every week dosing group, and 63 in the exploratory TDM group, based upon a 2:2:1 randomization scheme) from the 525 randomized induction subjects. This sample size would provide 80% power to detect a treatment difference of 18%, assuming an expected Week 52 remission rate of 48% in the adalimumab weekly dosing group and 30% in the adalimumab every other week dosing group.

Considering the uncertainty in the Week 8 response rate may be caused by the impact of central reading on the endoscopic subscore, based on the ozanimod Phase 2 TOUCHSTONE trial data presented in early 2015, AbbVie re-estimated the Week 8 response rate to be 50% instead of 60%. Under this assumption, if the sample remains 525, a smaller size of the Week 52 analysis set than was original predicted, and thus an insufficient power (72%) for the analysis of the Week 52 remission endpoint is expected. Furthermore, Week 52 remission rate will be the primary endpoint of the Maintenance Study. AbbVie proposes to increase the power for this endpoint from 80% as originally designed to 90% retaining the currently assumed treatment difference. The combined impact of these changes (i.e., increased power plus higher uncertainty in Week 8 response rate) results in an increase in the overall Study M14-033 sample size from 525 subjects to a total of 840 subjects.

Subjects will be randomized to the adalimumab higher induction regimen and the adalimumab standard induction regimen in a 3:2 ratio. The sample size calculations for the main study are based on a two sided Fisher's exact test at a significance level of 0.05. Assuming an expected Week 8 endoscopic improvement rate of 60% in the adalimumab

higher induction dosing regimen and 45% in the adalimumab standard induction dosing regimen, 804 subjects (504 subjects in the higher induction dosing regimen and 336 subjects in the standard induction dosing regimen) will provide 90% statistical power to detect the difference between the two induction treatment regimens. This sample size of 804 subjects in the main study will provide at least 95% power to detect a treatment difference of 15% for the primary endpoint of clinical remission, assuming an expected Week 8 clinical remission rate of 35% in the adalimumab higher induction regimen and 20% in the adalimumab standard induction regimen.

Assuming the average response rate at Week 8 in the adalimumab induction dosing regimens in the main study is 50%, there will be 420 responders for the analysis of Week 52 clinical remission among the Week 8 responders (168 in the higher maintenance dosing regimen, 168 in the standard maintenance dosing regimen, and 84 in the TDM regimen). This sample size will provide 90% power to detect a treatment difference of 18%, assuming an expected Week 52 clinical remission rate of 48% in the adalimumab higher maintenance dosing regimen and 30% in the adalimumab standard maintenance dosing regimen.

The sample size calculations for the Japan sub-study are described in Appendix K.

8.3 Randomization Methods

At Baseline, subjects will be randomized 3:2 to one of two double-blinded adalimumab induction regimens (higher dose or standard dose). The randomization will be stratified by previous infliximab use and Baseline corticosteroid use. In both the main study and the Japan sub-study populations, up to 25% of subjects with previous infliximab exposure may be enrolled.

At the conclusion of the 8-week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study. Re-randomization will be stratified by induction treatment regimen and response status (per Full Mayo Score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. Among Week 8 responders, the

randomization will be further stratified by remission status (per Full Mayo Score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. All subjects will be randomized into one of three blinded treatment regimens in a 2:2:1 ratio:

- Adalimumab 40 mg eow
- Adalimumab 40 mg ew
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory). (The Japan sub-study does not have a TDM regimen. Subjects will be randomized into Adalimumab 40 mg eow or Adalimumab 40 mg ew treatment regimens in a 1:1 ratio.)

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)

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.

Any optional testing will only be performed if the subject has voluntarily given 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. Subject consent must be signed before the optional testing is performed. If the subject does not consent to the optional testing, it will not affect 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.

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.

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

CRFs 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. eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system, except for subject-completed questionnaires, which will be completed on paper by the subject then transcribed into the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or AbbVie's representatives). AbbVie (or AbbVie's 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
- SF-36 acute recall version 2.0
- WPAI

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 documentation.

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 (stool frequency, abdominal discomfort, number of bloody stools, fecal urgency, use of anti-diarrheals, use of medications used for endoscopy preparation, general well-being and dosing information) 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. The subject's dosing information will be used as confirmation for the site and site staff will need to add the information to the appropriate eCRF. To calculate the Partial Mayo score, the site will be able to use the subscores from ePRO to manually enter into the eCRF.

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.

Data from the central laboratory and the imaging vendor will be electronically transferred to the study database.

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

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or AbbVie's 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 Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol Date:	16 June 2016

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (printed or typed)

15.0 Reference List

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15. YAKUSHOKUSHINSA Notification No. 0928010 dated on September 28, 2007, issued by Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare.

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
		Clinical
		Data and Statistical Sciences
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical
		Bioanalysis

Appendix C. Script for Collection of Mayo Scores for Use in Study M14-033

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

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

Stool Frequency Subscore

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

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

A number of bowel movements lower than or equal to the reference number of bowel movements should be scored as 0 = Normal.

One or 2 bowel movements more than the reference number of bowel movements should be scored as 1.

> Three or 4 bowel movements more than the reference number of bowel movements should be scored as 2.
>
> Five or more bowel movements more than the reference number of bowel movements should be scored as 3.

The Stool Frequency subscores based on 5 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit.

The Stool Frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3.

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

Rectal Bleeding Subscore

Subjects will be assigned a daily rectal bleeding subscore value as follows:

No visible blood with stool during the respective day should be scored as 0.

Visible blood with stool less than half the time during the respective day should be scored as 1.

Visible blood with stool at least half the time during the respective day should be scored as 2.

A score of 3 for bleeding requires subjects to have at least 50% of bowel movements accompanied by visible blood and at least one bowel movement with blood alone.

The score entries into subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit.

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

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

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the 2 subject-reported subscores, the endoscopy subscore as applicable, the subject's daily record of abdominal discomfort and general well-being during based on the 5 days prior to the visit, and other observations such as physical findings, and the subject's performance status in order to assess disease activity as follows:

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Endoscopy Subscore

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

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

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

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

The endoscopy will be recorded (not a still image) and will undergo a central review process for endoscopy subscore assessment.

Sources: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-ASA therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987;317(26):1625-9.

Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the Mayo Score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008;14(12):1660-6.

Appendix D. Sample WPAI Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis V2.0 (WPAI:UC)

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

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

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

2. During the past seven days, how many hours did you miss from work because of problems associated with your ulcerative colitis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your ulcerative colitis. 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 ulcerative colitis affect your productivity while you were working?

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

Consider only how much ulcerative colitis affected productivity while you were working.

Ulcerative colitis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Ulcerative colitis completely prevented me from working

CIRCLE A NUMBER

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

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

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

Ulcerative colitis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Ulcerative colitis completely prevented me from doing my daily activities

CIRCLE A NUMBER

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Appendix E. Sample Injection Instructions – Pre-Filled Syringe

Subject Instructions

0.8 mL dose

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

Protocol M14-033

Tables of Contents

Dosing Schedule

General Information and Supplies

Injection Procedures

Study Drug Dosing Schedule

Subject Number: _____

You will require subcutaneous injections throughout the study.

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

- Baseline visit (the first visit to receive study medication for this study), Week 1 and Week 2 you will receive 4 injections (2 kits) at the clinic.
- Week 3 you will administer 4 injections (2 kits) at home.
- Weeks 4, 8, 10, 12, 16, 22, 29, 35, 42, and 48 you will receive 1 injection at the clinic.
- Weeks 6, 9, 11, 13, 14, 15, 17-21, 23, 25-28, 30 – 34, 36, 38 –41, 43 – 47, and 49 – 51 you will administer 1 injection at home.
- Weeks 24 and 37 you will receive 4 injections at the clinic.

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.

Remember to complete your 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:

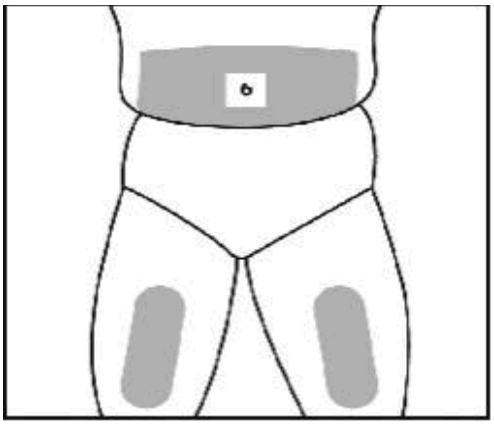
- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

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

INSTRUCTIONS FOR SELF-ADMINISTERED INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (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 graded response choices numbered from 1 to 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 nurse questions after completing the questionnaire. This takes only a few minutes to complete.

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 Ulcerative Colitis 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 2 weeks? Please indicate how frequent your bowel movements have been during the last 2 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

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. 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

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

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

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

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

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IBDQ – United Kingdom-English – Version of 09 May 08 – Mapi Research Institute.
ID4529/IBDQ_AU2.0_eng-GB.doc

Appendix G. Sample SF-36 v2 Acute, US Version 2.0

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
[a] Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
[b] Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
[c] Lifting or carrying groceries	☐1	☐2	☐3
[d] Climbing several flights of stairs	☐1	☐2	☐3
[e] Climbing one flight of stairs	☐1	☐2	☐3
[f] Bending, kneeling, or stooping	☐1	☐2	☐3
[g] Walking more than a mile	☐1	☐2	☐3
[h] Walking several hundred yards	☐1	☐2	☐3
[i] Walking one hundred yards	☐1	☐2	☐3
[j] Bathing or dressing yourself	☐1	☐2	☐3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
[a] Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
[b] Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
[c] Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
[d] Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
[a] Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
[b] Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
[c] Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
[a] Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
[b] Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
[c] Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
[d] Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
[e] Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
[f] Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
[g] Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
[h] Have you been happy?	☐1	☐2	☐3	☐4	☐5
[i] Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
[a] I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
[b] I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
[c] I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
[d] My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS

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Appendix H. 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.

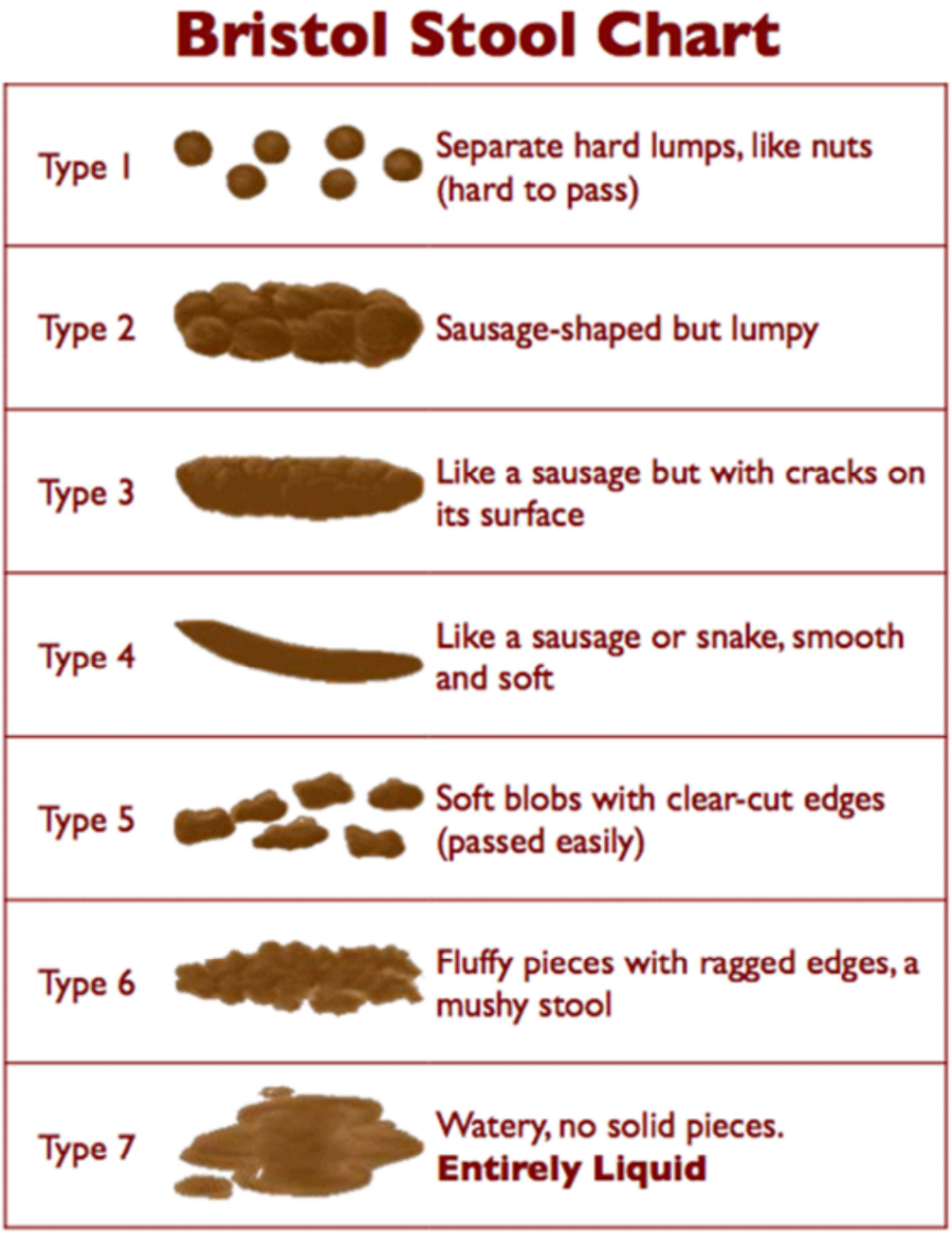
Loss of Response

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 I. Sample Bristol Stool Chart



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

Site Name/Site Number: _____

Subject Number: _____

Date of last study drug administration (DD/MMM/YY): _____

Please contact subjects who discontinue adalimumab 70 days following study drug discontinuation.

Note: Subjects who continue commercial adalimumab do not require a 70-day follow-up call.

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
- ☐ AEs/SAEs Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.) Any medications taken as a result of the events should also be entered on the eCRF.

_____

_____

_____

_____

_____

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

If 70-day follow-up call was not performed:

- ☐ Subject continued adalimumab therapy after the end of their study participation
- ☐ Other, describe below: _____

_____

_____

_____

_____

Please fax all completed forms to:

Fax: [redacted]

Email: [redacted]

Subject line: PI NAME_Subject number_70 day followup

Appendix K. Japan Sub-Study

There will be a Japan sub-study that includes only Japanese subjects enrolled from sites in Japan. The subjects enrolled under the Japan sub-study will not be included in the primary analyses of the main study nor used for regulatory applications outside of Japan. The Japan sub-study will, however, allow the integration of clinical data obtained from all other subjects in the main study to support a future regulatory application in Japan.

The main study is to be followed for the Japan sub-study except where indicated as outlined below.

4.0 Study Objective of Japan Sub-Study

The study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis and to show the consistency of efficacy between Japanese population and integrated population of Japanese and western subjects.

5.0 Investigational Plan of Japan Sub-Study

5.1 Overall Study Design and Plan: Description

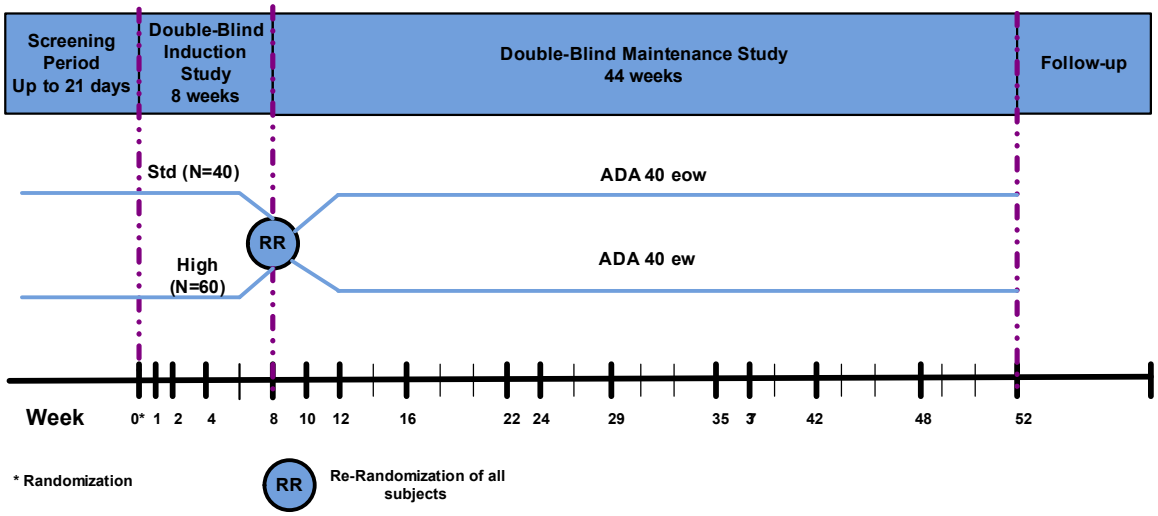
The primary analysis for the Japan sub-study during the Induction Study will be an analysis of subjects achieving clinical remission (per Full Mayo Score) at Week 8. The primary analysis for the Japan sub-study during the Maintenance Study will be an analysis of subjects is the proportion of Week 8 responders achieving clinical remission (per Full Mayo score) at Week 52.

The analysis will include approximately 100 subjects (60 in the higher induction dose regimen and 40 in the standard induction dose regimen) from 21 Japanese sites and approximately 840 subjects from all other sites in the main study.

44-Week Double-Blind Maintenance Study

The TDM regimen in the maintenance period will not be applied to the Japan sub-study because of logistical challenges in obtaining adalimumab serum concentration results within the time period specified in the main study. At the conclusion of the 8-Week Double-Blind Induction Study, subjects will return to the study site and will be re randomized using the same stratification variables as the main study via IRT into the 44-Week Double-Blind Maintenance Study to one of two treatment groups in a 1:1 ratio with the same stratification from the main study:

- Adalimumab 40 mg eow
- Adalimumab 40 mg every week (ew)



Subjects in the adalimumab 40 mg eow treatment group will continue to receive 40 mg eow until the end of the study. Subjects in the adalimumab 40 mg ew treatment group will start 40 mg ew at Week 8 until the end of the study.

5.2.1 Inclusion Criteria

Differences from main study are underlined.

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol. If the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.
2. Japanese male or female ≥ 18 and ≤ 75 years of age at the Baseline visit.
3. Subject with a diagnosis of Ulcerative Colitis for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period with exclusion of infection, current dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.
4. Active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) 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 or immunosuppressants as defined below):
   - Subject taking oral corticosteroids, excluding budesonide or beclomethasone:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subject 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 subject 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 subject 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 subject 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.
   - Subject taking oral beclomethasone:

- Dose must not exceed 5 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.

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 for their UC from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of UC related symptoms) or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed

infusion/administration reaction to the medication). Confirmed documentation indicating loss or response or lack of tolerability will be required, see Section 10.1 and Appendix H.

6. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly 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;
   - A 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.
7. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.
8. Subject has a negative TB Screening Assessment. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 21 days of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline (see Section 5.3.1.1).
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, chest x-ray, and a 12-lead ECG performed during Screening.
10. Subject must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

Rationale for the Difference from Main Study:

The lower doses of azathioprine and 6-MP are recommended for Japanese IBD patients because of the difference of TPMT activity between Japanese and western IBD patients. The 6-TGN (active metabolite of azathioprine and 6-MP) concentration in Japanese patients with IBD on the specified doses of azathioprine and 6-MP therapy is considered to be comparable to those reported from Western countries.

5.2.2 Exclusion Criteria

Differences from main study are underlined.

1. Subject with diagnosis and/or history of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
7. Positive pregnancy test at Screening (serum) or Baseline (urine).
8. Female who is breast-feeding or considering becoming pregnant during the study.
9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subject on azathioprine, 6-MP, 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.

11. Subject on oral aminosalicylates who:
    - Has not been on stable doses of these medications for at least 14 days prior to Baseline; or
    - Has discontinued use of aminosalicylates within 14 days of Baseline.
12. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subject on oral budesonide > 9 mg/day; or subject on oral beclomethasone > 5 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 of at least 14 days in duration 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 oral 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 of at least 14 days in duration 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 has **not** been a current steroid course of at least 14 days in duration prior to Baseline; or
    - Subject taking oral beclomethasone:
        - has **not** been on a stable dose for at least 7 days prior to Baseline; or

- but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline; or

Has been taking, both oral budesonide (or oral beclomethasone) and oral prednisone (or equivalent) simultaneously.

and/or

Has discontinued use of corticosteroids within 14 days of Baseline

13. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.

14. Positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening Period.

15. Currently receiving total parenteral nutrition (TPN).

16. Subject who received any investigational agent or procedure (including previous fecal microbial transplantation) within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer.

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

18. 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.

19. 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®]) or previous participation in an adalimumab clinical study. Prior exposure to any anti-TNF agent other than infliximab (including but not limited to adalimumab

[Humira®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).

20. Subject with known hypersensitivity to the excipients of adalimumab as stated in the prescribing information.

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

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

23. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).

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

25. Subjects with a positive result for 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.

26. Chronic recurring infections or active TB.

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

28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

29. 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.

30. Received cytoapheresis treatment (GCAP, LCAP etc.) within 8 weeks prior to Baseline.

31. Received ATM treatment (antibiotic combination therapy with amoxicillin, tetracycline and metronidazole) during the Screening Period.

Rationale for the Difference from Main Study:

Concomitant therapies for UC (cytoapheresis treatment and ATM therapy) that are possibly used in Japan should be prohibited to avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments.

5.2.3.3 Prohibited Therapy

In Japan, the following therapies are also prohibited during the study:

- Cytoapheresis treatment (GCAP, LCAP etc.)
- ATM treatment (antibiotic combination therapy with amoxicillin, tetracycline and metronidazole)

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 into the study.

Table 2. Study Activities

Activity	Screening Period (21 days)	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Informed Consent	X																		
Inclusion/Exclusion	X	X[b]																	
Medical/Surgical History	X	X[b]																	
Previous and Concomitant Medication	X	X[b]	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	X	
Schedule Endoscopy	X				X											X			
Endoscopy/Biopsy[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/Hematology[i]	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	
Urinalysis[i,j]	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	

Table 2. Study Activities (Continued)

Activity	Screening Period	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Pregnancy Test[k]	X	X															X		
Hepatitis B Screen, HIV[l]	X																		
hs-CRP	X	X				X		X	X		X	X		X	X		X	X	
C. difficile Toxin	X																		
Provide Stool Kit [m]	X				X		X	X		X			X			X			
Stool Sample (Fecal Calprotectin)[m]	X					X		X	X		X			X			X		
Stool Sample (Microbiota Metagenomic Analysis)[m]	X					X			X		X						X		
Bristol Stool Chart [m]	X					X			X		X						X		
Antinuclear antibody (ANA)/ Anti-Double-Stranded DNA (anti-dsDNA)[n]	X																		
Human Antichimeric Antibodies (HACA)/ Infliximab Concentrations		X																	

Table 2. Study Activities (Continued)

Activity	Screening Period	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Adalimumab Concentration[o]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AAA Concentration[o]		X			X	X		X			X			X			X	X	
Pharmacogenetic (optional)[p]		X															X		
Serologic Markers/mRNA		X		X	X	X					X						X		
Inflammatory Bowel Disease Questionnaire (IBDQ)		X		X	X	X		X			X			X			X		
Partial Mayo Score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mayo Score		X				X											X		
SF-36		X				X											X		
Work Productivity and Impairment Questionnaire (WPAI)		X				X											X		

Table 2. Study Activities (Continued)

Activity	Screening Period	8-Week Double-Blind Induction Study					44-Week Double-Blind Maintenance Study											Unscheduled Visit[v]	70-Day Follow-Up[u]
	Screening	Baseline (Week 0)[a]	Week 1	Week 2	Week 4	Week 8 (Re-Randomization)	Week 10	Week 12	Week 16	Week 22	Week 24	Week 29	Week 35	Week 37	Week 42	Week 48	Week 52/Premature Discontinuation		
Start Corticosteroid Taper[q]					X														
Monitor Adverse Events[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Daily Diary[s]	X																		
Daily Diary[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject Trained on Self-Administration of Injections		X																	
Study Drug Dispensing/ Administration[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

a. The 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.

Table 2. Study Activities (Continued)

d. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy for histologic assessment during Screening, at Week 8 and at Week 52/PD (for subjects who remain in the study through at least Week 24). A full colonoscopy will be performed at Screening unless the subject underwent a full colonoscopy within 12 months prior to Screening and appropriate documentation is available (to confirm the diagnosis and extent of disease and no evidence of dysplasia and colon cancer). In this case, the screening endoscopy may be either a full colonoscopy or a flexible sigmoidoscopy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, 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 colon must be performed during the Screening endoscopy and evaluated by a qualified local pathologist and the results reviewed by the Investigator. Biopsies to rule out dysplasia and colon cancer may be taken during any study endoscopy per the Investigator's discretion and evaluated by the local pathologist. The Week 8 and Week 52/PD endoscopies may be either full colonoscopies or flexible sigmoidoscopies. During all endoscopies, 2 biopsies for histologic evaluation by a central laboratory will be taken from each observed colonic segment (see Section 5.3.1.1 for details about biopsy sampling).

e. Physical examinations performed at Screening, Week 8 and Week 52/PD Visits are full physical examinations which must include an assessment of extra-intestinal manifestations (EIMs). Physical exams performed at all other visits are symptom-based.

f. Subjects with negative latent TB test(s) (In cases where a subject received both a PPD test and IGRA, both must be negative) within 90 days of Screening will not require a repeat latent TB 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 will not require a repeat chest x-ray, if documentation is available.

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

i. Laboratory 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. A serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy test will be performed at Baseline Visit, and at the Week 52/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 Section 5.3.1.1 in the Hepatitis B testing section 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.

Table 2. Study Activities (Continued)

m. 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 the site. 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. Remaining sample will be stored for potential research testing.

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

o. Blood samples for the measurement of adalimumab, AAA concentrations, serologic markers and mRNA will be collected prior to dosing. **Note:** 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.

p. Verify subject has signed consent for optional pharmacogenetic sample prior to the sample drawn. If the sample is not collected at Baseline, preferably it should be collected at the next study visit.

q. Subjects will begin the 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 Serious Adverse Events (SAEs) begins the day the subject signs the informed consent.

s. Subjects will be dispensed the subject 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, including during hospitalizations whenever possible. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD visit.

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

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

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 and assessment of ulcerative colitis.

5.3.2 Drug Concentration Measurements

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 22 samples (not including unscheduled visit sample collections) are planned in Japan to be collected per subject for adalimumab (15 samples) and AAA (7 samples) assays. The total number of samples planned (not including unscheduled visit sample collections) will not exceed 1,500 (15 samples × 100 subjects) for the adalimumab assay and 700 (7 samples × 100 subjects) for the AAA assay for the sub-study.

Collection of Samples for Infliximab and HACA Assays

Blood samples for infliximab and HACA assay will be collected at Week 0 (Baseline) by venipuncture into appropriately labeled 4-mL evacuated serum collection tube without gel separator at Baseline. 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 for Japan will not exceed 200 (2 samples × 100 subjects) for the sub-study.

5.5.1 Treatments Administered

Double-Blind Induction Study

At Baseline (Week 0), subjects will be randomized 3:2 to one of two double-blind adalimumab induction regimens.

Subjects assigned to the standard induction regimen will receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and matching placebo (4 syringes) at Week 1. At Week 2, subjects will receive 80 mg (2 syringes) and matching placebo (2 syringes). At Week 3, subjects will receive matching placebo (4 syringes) and at Weeks 4 and 6, subjects will receive a dosing regimen of 40 mg (1 syringe).

Subjects assigned to the higher induction regimen will receive 160 mg (4 syringes) at Weeks 0, 1, 2, and 3 followed by 40 mg (1 syringe) at Weeks 4 and 6.

Double-Blind Maintenance Study

At Week 8, subjects will be re-randomized to receive 1 of 2 double-blind adalimumab treatment maintenance regimens in a 1:1 ratio.

Subjects assigned to the adalimumab 40 mg eow regimen will receive 40 mg (1 syringe) at Weeks 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and 50. Matching Placebo (1 syringe) will be administered at Weeks 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects assigned to the adalimumab 40 mg ew regimen will receive 40 mg (1 syringe) at Weeks 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

5.5.3 Method of Assigning Subjects to Treatment Regimens

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 Week 0 in a 3:2 ratio into the criteria-driven regimens using the IRT, which will assign a randomization number according to the randomization scheme, generated by AbbVie before the start of the study. The randomization will be stratified by previous infliximab

use and Baseline corticosteroid use. The criteria-driven regimen assignment will be maintained by the IRT. Subjects will be referred to by the subject number assigned at Screening.

Subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Study at the conclusion of the Week 8 Visit to one of two treatment regimens in a 1:1 ratio. Subjects will be re-stratified by: induction treatment regimen and response status (per Full Mayo Score) at Week 8. Among Week 8 responders, the randomization will be further stratified by remission status (per Full Mayo Score) at Week 8.

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 IRT will be provided to each site. Study drug will be dispensed/administered at the study visits summarized in Table 2.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 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 SAE or non-serious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® system or if RAVE® is not operable, should be documented on the SAE Non-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: [redacted]

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

Primary Study Designated Physician

[redacted] MD
Immunology Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

Contact Information:
Phone: [redacted]
Mobile:
Fax:
Email:

Secondary Contact for Japan (Regional Medical Monitor)

[redacted] MD, PhD
[redacted] Japan Development
AbbVie GK
3-5-27 Mita, Minato
Tokyo, 108-6302
Japan

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) or secondary Japan contact 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 Humira Investigator's Brochure.

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

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 IEC/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned CRO Clinical Monitor or the following AbbVie Clinical Monitor(s):

CRO Contact:

[redacted]
Linical Co., Ltd.
1-6-1, Miyahara, Yodogawa-ku, Osaka 532-0003, Japan
Office: [redacted]
Fax:
Email:

AbbVie Contact:

[redacted]
AbbVie GK
3-5-27, Mita, Minato-ku, Tokyo 108-6302, Japan
Office: [redacted]
Fax:
Email:

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.

The Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses of the Japan sub-study are to evaluate the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis in the Japanese sites and all sites from both the main study and the Japan sub-study. Efficacy analysis will be

performed in the integrated Intent to Treat (ITT1) set and the Japan ITT1 set. The safety analysis will be conducted in the integrated Safety set and the Japan Safety set, using the population defined in Section 8.1.1. A separate detailed statistical analysis plan (SAP) will be completed prior to database lock of the main study and the Japan sub-study.

8.1.1 Analysis Population

The integrated ITT1 (I-ITT1) dataset includes all randomized subjects (at both Japanese sites and all other sites in the main study). The Japan ITT1 (J-ITT1) dataset includes all subjects who were randomized at Japanese sites only and will be used for efficacy analyses of Japanese subjects separately from other subjects in the main study. The integrated Intent to-Treat maintenance (I-ITT2) population includes all subjects (at both Japanese sites and all other sites in the main study) who are re randomized to 40 mg eow group and 40 mg ew group at Week 8 (subjects who are re-randomized to TDM group will not be included). The I-ITT2 subjects will be analyzed as randomized. The I-ITT2 is the primary population for the efficacy analysis at Week 52 during the maintenance study.

The J-ITT2 dataset includes all subjects who were re-randomized at Week 8 at Japanese sites only and will be used for maintenance efficacy analyses of Japanese subjects separately from other subjects in the main study.

The integrated Safety set consists of all subjects (from both Japanese sites and those sites following the parent protocol) who received at least one dose of study medication. The Japan Safety set consists of all randomized subjects from Japanese sites who received at least one dose of study medication.

8.1.3 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized similarly as the main study for each treatment group using descriptive statistics in both the I-ITT1 dataset and the J-ITT1 dataset. The p-value will be provided to assess the comparability of the treatment groups assigned by randomization. Continuous variables

will be analyzed using analysis of variance (ANOVA) and discrete variables will be analyzed using chi-square test or Fisher's exact test.

8.1.4 Statistical Analysis of Efficacy

8.1.4.1 Primary Efficacy Variables

The primary efficacy endpoint for the Induction Study is:

Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

The primary endpoint for the Induction Study will be analyzed similarly as the main study using the I-ITT1 and J-ITT1 sets. The difference between the treatment groups in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method). Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non-responders.

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint for the Induction Study.

For primary analysis of the Maintenance Study will compare the Week 8 responders (per Full Mayo Score) in the eow regimen versus the subjects in the ew regimen in the I-ITT2 and J-ITT2 analysis sets. The difference between the treatment regimen in the proportion of subjects achieving clinical remission at Week 52 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for Induction treatment regimen and the remitter status (per Full Mayo Score) at Week 8. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 52 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 52 endpoint. Subjects with missing Mayo score data for Week 52 will also be classified as Week 52 non-responders.

8.1.4.2 Secondary Efficacy Variables

The analysis for secondary efficacy variables will be performed similarly as the main study using the I-ITT1 set and the J-ITT1 set for Induction Study endpoints at Week 8, or the I-ITT2 set and the J-ITT2 set for Maintenance Study endpoints at Week 52, where appropriate.

8.1.5 Statistical Analysis of Safety

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study and will be analyzed similarly as the main study for the integrated Safety set and the Japan Safety set.

8.1.7 Interim Analyses

An interim analysis of the primary endpoint and ranked secondary efficacy variables for Week 8 only as well as safety data collected from Baseline through double-blind Week 8 will be performed only if performed for the main study.

8.2 Determination of Sample Size of Japan Sub-study

Section 8.2 of the main study outlines the rationale for the sample size of 840 subjects. An additional 100 subjects has been determined as the proper sample size for the Japan sub-study based on the following rationale.

Using the same assumptions as the main study with the following:

- Remission rate for induction treatment at 8 weeks: 35% in the high dose group and 20% in the standard dose group
- Remission rate for maintenance treatment at 52 weeks among Week 8 responders: 48% in the high dose group and 30% in the standard dose group
- Overall response rate for induction treatment at Week 8: 50%
- $\alpha = 5\%$, power = 95% for induction study
- $\alpha = 5\%$, power = 90% for maintenance study

The precisions of point estimations of remission rates in Japanese population are included within the 95% CI of remission rates in integrated population will be within 20% with 100 subjects. With this sample size, the probability to show consistency between Japanese population and integrated population will be greater than 80% using the method 2 shown in the "Basic principles on global clinical trials."[15]

8.3 Randomization Methods

At Baseline, subjects will be randomized 3:2 to one of two double-blinded adalimumab induction regimens (higher dose or standard dose). The randomization will be stratified by previous infliximab use and Baseline corticosteroid use. At the conclusion of the 8-week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study. Re-randomization will be stratified by induction treatment regimen, and response status (per Full Mayo Score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. Among Week 8 responders, the randomization will be further stratified by remission status (per Full Mayo Score utilizing the Week 8 endoscopy subscore

provided by the site) at Week 8. All subjects will be randomized into one of two blinded treatment regimens in a 1:1 ratio:

- Adalimumab 40 mg eow
- Adalimumab 40 mg ew

The randomization schedules will be prepared separately for the Japan sub-study by the Statistics Department of AbbVie.

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. If the subject is < 20 years old, a subject's parent or legal guardian must be explained and willing to give written informed consent. 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.

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 be withdrawn. 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 still remain as part of the overall research data.

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.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the Principal Investigator will revise without delay the consent form and explanatory material based on the information and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue in the study or not. The Investigator will also provide further explanation using the revised consent form and explanatory material and will obtain written consent from each subject of their own free will to continue participating in the study. If the subject is < 20 years old, a subject's parent or legal guardian must be explained and willing to give written informed consent.

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 Director of the Site and the Sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Director of the Site and the Sponsor. The investigator will provide a final report to the Director of the Site following conclusion of the study, and the Director of the Site will inform the summary of the report to IRB and the Sponsor.

The Director of the Site must retain any records related to the study according to local requirements. If the Director of the Site is not able to retain the records, he/she must notify the Sponsor 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 Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

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

16.0 Clinical Expense and Compensation

16.1 Expenditure of the Clinical Expense

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses of screening test, etc. will be paid based on the contract concluded with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

16.2 Compensation for Health Impairment and Insurance

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and take other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might occur between the investigative site and the subject, the investigative site will immediately report this to the sponsor and resolve it. The sponsor will cooperate with the investigative site in resolving any issues or problems.

3. When the investigative site must compensate subject for any health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by the investigative site.
4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.
5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

17.0 Storage of Records

The directors of the investigation sites will retain the "Essential documents to be retained by study institutions" specified in the Section 4.9.5 of ICH guideline for the period specified the following.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Appendix L. 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:

Sponsor/Emergency Contact:	**All Participating Countries** [redacted] MD [redacted] AbbVie Deutschland GmbH & Co. KG Knollstrasse 50 67061 Ludwigshafen, Germany Office: [redacted] Mobile: Fax: Email: **Secondary Japan Contact:** [redacted] MD, PhD [redacted] Japan Development AbbVie GK 3-5-27 Mita, Minato Tokyo, 108-6302 Japan Office: [redacted] Mobile: Fax: Email:

Has been changed to read:

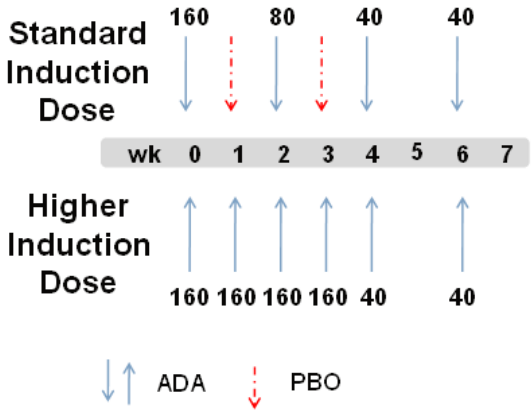
Sponsor/Emergency Contact:	**All Participating Countries** [redacted] MD [redacted] Immunology Development AbbVie Deutschland GmbH & Co. KG Knollstrasse 50 67061 Ludwigshafen, Germany Office: [redacted] Mobile: Fax: Email: **Secondary Japan Contact:** [redacted] MD, PhD [redacted] Japan Development AbbVie GK 3-5-27 Mita, Minato Tokyo, 108-6302 Japan Office: [redacted] Mobile: Fax: Email:

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-033
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 03 December 2015
Protocol Title: A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis	
Objective: The primary objective is to evaluate safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active Ulcerative Colitis (UC).	
Investigators: Multicenter Trial (Investigator information on file at AbbVie).	
Study Sites: Approximately 125 sites for the main study and approximately 21 sites for the Japan sub-study.	
Study Population: Male and female subjects ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active UC (up to 25% infliximab-experienced).	
Number of Subjects to be Enrolled: For the main study, approximately 525 subjects (315 in the higher induction dose regimen and 210 in the standard induction dose regimen) will be enrolled at approximately 125 sites worldwide. There also will be 80 Japanese subjects (48 in the higher induction dose regimen and 32 in the standard induction dose regimen) in a Japan sub-study to be enrolled at 21 Japan sites. In both the main study and Japan sub-study, up to 25% of subjects with previous infliximab exposure may be enrolled.	
Methodology: This Phase 3 study design includes a Screening Period, an 8-Week Double-Blind Induction Period and a 44-Week Double-Blind Maintenance Period. Subjects will have moderately to severely active UC as defined by a Mayo Score of 6 to 12 points with an endoscopy subscore of 2 or 3, confirmed by a central reader. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the 8-week Induction Period. For all Mayo Score evaluations throughout the study, the stool frequency and the rectal bleeding subscores will be calculated based on entries recorded into the subject's diary based on 5 days prior to each study visit. During the Induction Period, subjects will be randomized at Baseline to one of 2 double-blinded adalimumab induction regimens (higher dose or standard dose) in a 3:2 ratio, as shown in the following figure. Use of the 3:2 randomization scheme allows for collection of additional safety data with the higher induction dose regimen. The randomization will be stratified by previous infliximab use and Baseline corticosteroid use.	

Methodology (Continued):

8-Week Double-Blind Induction Period



The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6 leads to a total adalimumab dose over 8 weeks that is approximately twice that of the standard induction dose regimen (720 mg versus 320 mg). The higher induction dose regimen was designed for rapid attainment of higher adalimumab serum concentrations in order to rapidly control inflammation. Pre-dosing serum samples for infliximab concentration and human antichimeric antibodies (HACAs) will be collected at Week 0. Pre-dosing serum samples for adalimumab drug levels will be collected at Weeks 0, 2, 4, and 8. Pre-dosing serum samples for anti-adalimumab antibodies will be collected at Weeks 0, 4, and 8.

At Week 4, all subjects who are on oral steroids will have their steroid dose tapered according to the proposed tapering schedule outlined in the 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.

At the conclusion of the 8-Week Induction Period, all subjects will be re-randomized into the 44-week Maintenance Period. Re-randomization will be stratified by induction treatment regimen and response status (per Full Mayo Score) at Week 8. Among the responders at Week 8, the randomization will be further stratified by remission status (per Full Mayo score) at Week 8. All subjects in the main study will be randomized into one of three blinded treatment arms in a 2:2:1 ratio:

- Adalimumab 40 mg every other week (eow)
- Adalimumab 40 mg every week (ew)
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory arm)*

* 1) All subjects in the TDM arm will receive 40 mg eow at Week 8 and Week 10. At Weeks 12, 24, and 37, the regimen will be adjusted for subjects meeting the dose adjustment criteria (see table below) based on blinded serum concentrations at the prior visit (Weeks 10, 22 and 35, respectively) and rectal bleeding subscore at the prior and current visits as follows:

- Subjects receiving 40 mg eow who meet the dose adjustment criteria will escalate to 40 mg weekly.
- Subjects receiving 40 mg ew who meet the dose adjustment criteria will receive a one-time dose of 160 mg at the visit, and resume 40 mg ew starting the following week.

Methodology (Continued):

2) Japan sub-study does not have TDM arm. Subjects will be randomized into Adalimumab 40 mg eow arm or Adalimumab 40 mg ew arm in a 1:1 ratio.

During the maintenance period, pre-dosing serum samples for adalimumab drug levels will be collected in all subjects at Weeks 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52/Premature Discontinuation (PD), and unscheduled visits. Pre-dosing serum samples for anti-adalimumab antibodies will be collected at Weeks 12, 24, 37, 52/PD, and unscheduled visits.

The goal of the TDM regimen is to attain serum adalimumab levels within a targeted concentration range (selected based on exposure-response analyses from Study M06-827) while avoiding excessively high concentrations. During maintenance therapy in Study M06-827, concentrations ranged from 0 to 39.3 µg/mL with eow dosing and 0 to 38.0 µg/mL with ew dosing. The lower bound (10 µg/mL) of the targeted concentration range for the TDM regimen is similar to the median concentrations observed over time for the subjects in remission at Week 52 of Study M06-827 (11.4, 10.6, and 10.8 µg/mL, for Weeks 8, 32, and 52, respectively). Use of this concentration as the minimum threshold to trigger dose escalation will lead to the majority of subjects achieving concentrations greater than 10 µg/mL. Since serum adalimumab concentrations roughly double with a doubling of dose, an upper bound of 20 µg/mL is expected to achieve maximal trough concentrations in the range of the highest trough concentrations observed in Study M06-827. It is expected that approximately 60% of subjects in the TDM arm will escalate to ew dosing and 15% or fewer will receive reinduction using this concentration range plus the Rectal Bleeding Subscore (RBS) criteria outlined in the table below as a guide to adjust adalimumab dosing.

TDM Arm Dose Adjustment Criteria[a]

Adalimumab Serum Concentration[b]	Rectal Bleeding Subscore[c]	Dose Escalate?[d]
< 10 µg/mL	Any	Yes
10 µg/ml to 20 µg/mL	< 1	No
10 µg/ml to 20 µg/mL	≥ 1	Yes
> 20 µg/mL	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. The score entries into the subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding Subscore for each study visit.

d. For subjects on 40 mg eow, escalate to 40 mg ew. Subjects on 40 mg ew will receive "reinduction" with a dose of 160 mg at the visit and resume 40 mg ew 1 week later.

Note: There will be no allowance for dose adjustment in the adalimumab eow or ew dosing arms.

Methodology (Continued)

Study visits for clinical and safety assessments will be performed at Baseline (Week 0), Weeks 1, 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, and 52/PD. All subjects will be provided with a Subject Diary where they will record ulcerative colitis-related symptoms (daily stool frequency, abdominal discomfort, number of bloody stools, fecal urgency, and general well-being), use of anti-diarrheals, use of medications for endoscopy preparation, and study drug dosing information throughout the study. Blood samples will be collected for hs-CRP, adalimumab serum concentrations, anti-adalimumab antibody (AAA) levels, and other biomarker analyses. In addition, stool samples for calprotectin and microbiota metagenomic analyses will be collected. The stool samples should be taken before starting bowel preparations for endoscopy. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy for histologic assessment during Screening, at Week 8 and at Week 52/PD (for subjects who remain in the study through at least Week 24) with local investigator assessment for Mayo endoscopic subscore confirmed by a central reader. The central reviewer scoring will be used for all efficacy assessments. The endoscopy subscore result from the central reviewer during the screening period will be used to evaluate the eligibility of a subject to enroll in the study.

Subjects who consent to participate in the optional pharmacogenetic (PG) analysis should have an additional blood sample drawn at Baseline and at Week 52/PD.

Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator. Subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable should contact the Study Designated Physician.

Throughout the study, subjects will only be allowed to change the dosage of UC-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 proposed tapering schedule specified in the Protocol. 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.
- 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 through the end of the study. These subjects will continue to be evaluated in the safety population.

Subjects in whom UC-related medications (defined as oral or rectal aminosalicylates, systemic or rectal corticosteroids, or systemic medications affecting the immune system, including thiopurines, MTX, and agents listed in the study exclusion criteria) 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 through the end of the study. These subjects will continue to be evaluated in the safety population.

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

Diagnosis and Main Criteria for Inclusion/Exclusion:

The following Inclusion/Exclusion criteria are for subjects enrolled in the main study. Separate Inclusion/Exclusion criteria for subjects recruited in Japan will be followed in the Japan sub-study.

Main Inclusion:

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
2. Male or female ≥ 18 and ≤ 75 years of age at the Baseline visit.
3. Subject with a diagnosis of UC for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period, with exclusion of current infection, dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.
4. Active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) 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 or immunosuppressants as defined below):
   - Subject taking oral corticosteroids, excluding budesonide or beclomethasone:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subject 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 subject 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 subject 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 subject 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.
   - Subject taking oral beclomethasone:
     - Dose must not exceed 5 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.

   or,
   - At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP) or injectable methotrexate (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.

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

Main Inclusion (Continued):

Note: If a subject is taking (both an oral corticosteroid and an immunosuppressant listed above) BOTH of the drugs need to meet the above dosing and duration of use criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline), however prior or current 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.

5. Subject may be included if they have previously experienced a benefit for their UC from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of UC related symptoms) or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly 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);
   - A 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.
7. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.
8. Subject has a negative tuberculosis (TB) Screening Assessment. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.
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, chest x-ray, 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.

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

Main Exclusion:

1. Subject with diagnosis and/or history of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
7. Positive pregnancy test at Screening (serum) or Baseline (urine).
8. Female who is breast-feeding or considering becoming pregnant during the study.
9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subject on azathioprine, 6-MP, 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.
11. Subject on oral aminosalicylates who:
    - Has not been on stable doses of these medications for at least 14 days prior to Baseline; or
    - Has discontinued use of aminosalicylates within 14 days of Baseline.
12. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subject on oral budesonide > 9 mg/day; or subject on oral beclomethasone > 5 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 of at least 14 days in duration 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 oral 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 of at least 14 days in duration 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 has **not** been a current steroid course of at least 14 days in duration prior to Baseline; or

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

Main Exclusion (Continued):

- Subject taking oral beclomethasone:
  - has **not** been on a stable dose for at least 7 days prior to Baseline; or
  - but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline; or

Has been taking both oral budesonide (or oral becomethasone) and oral prednisone (or equivalent) simultaneously

and/or

Has discontinued use of corticosteroids within 14 days of Baseline.

13. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
14. Positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening Period.
15. Currently receiving total parenteral nutrition (TPN).
16. Subject who received any investigational agent or procedure (including previous fecal microbial transplantation) within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer.
17. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
18. 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.
19. 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®]) or previous participation in an adalimumab clinical study. Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including but not limited to adalimumab [Humira®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).
20. Subject with known hypersensitivity to the excipients of adalimumab (see Protocol).
21. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
22. 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. If the Screening endoscopy shows evidence of current dysplasia or malignancy, subject may not be enrolled in the study.
23. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).
24. Subject with 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):

25. 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 (+)
26. Chronic recurring infections or active TB.
27. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and/or any other condition which would put the subject at risk by participation in the study.
28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
29. 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.

Investigational Products:	Adalimumab
Double-Blind Induction Doses: NOTE: In order to retain blinding across regimens, all subjects in the Standard Induction Dose Regimen will receive matching placebo injections in addition to the adalimumab injection at Weeks 1, 2 and 3.	Subjects will be randomized to receive one of 2 double-blind adalimumab induction regimens. Standard Induction Dose Regimen: 160 mg at Week 0 and matching placebo at Week 1. Subjects will receive 80 mg at Week 2 and matching placebo at Week 3. Subjects will receive 40 mg at Week 4 and Week 6. Higher Induction Dose Regimen: 160 mg at Weeks 0, 1, 2, and 3. Subjects will receive 40 mg at Week 4 and Week 6.

Double-Blind Maintenance Doses:	Subjects will be re-randomized to receive one of 3 double-blind adalimumab maintenance regimens. Adalimumab 40 mg eow Regimen: 40 mg every other week, starting at Week 8 until Week 50. Matching Placebo will be administered every other week, starting at Week 9 until Week 51. No dose will be administered at Week 52. Adalimumab 40 mg ew Regimen: 40 mg every week, starting at Week 8 until Week 51. No dose will be administered at Week 52. Adalimumab TDM Regimen: 40 mg eow at Week 8 and Week 10. Matching placebo at Week 9 and Week 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria. Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly. Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week. Subjects receiving 40 mg eow who do not meet the regimen adjustment criteria will receive adalimumab 40 mg eow and placebo at alternative weeks. No dose will be administered at Week 52. NOTE: In order to retain blinding across regimens, all subjects in the 40 mg eow and 40 mg ew regimen arms and subjects who do not meet the criteria for dose escalation in the TDM regimen arm will receive matching placebo injections in addition to the adalimumab injection (placebo reinduction) at Weeks 24 and 37.
Mode of Administration:	Subcutaneous injection (SC)

Duration of Treatment: The treatment period is 52 weeks (8 weeks of induction therapy followed by 44 weeks of maintenance therapy). There will be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely. The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

Criteria for Evaluation:

The following analysis is for subjects recruited in the main study. A separate statistical analysis will be performed for subjects recruited in the Japan sub-study and for all subjects recruited in the main study and the Japan sub-study.

Efficacy:

For Week 8 endpoints, this study will compare the subjects in the higher adalimumab induction dose regimen versus the standard adalimumab induction dose regimen. For Week 52 endpoints, this study will compare the subjects in the eow regimen versus the ew regimen. The TDM regimen will be used for exploratory analyses.

The primary efficacy endpoint is:

- Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) include:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.

Criteria for Evaluation (Continued):

Efficacy (Continued):

2. Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
4. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
5. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.
7. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
8. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
9. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
10. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.
11. Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 8.
12. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 52.
13. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
14. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
15. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.
16. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.
17. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
18. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

Additional pre-specified endpoints include but are not limited to the following:

- Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.
- Assessment of the relationship between adalimumab serum concentrations and efficacy during induction and maintenance by Week 8 response status.
- Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.
- Proportion of subjects who are taking corticosteroids at Baseline and are steroid-free over time.

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.
- Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score ≤ 2 with no subscore > 1) score over time.
- Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of ≥ 2 points and ≥30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) over time.
- Change from Baseline in hs-CRP over time.
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in IBDQ score over time.
- Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.
- Change from Baseline in SF-36 score over time.
- Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic improvement at Week 52.
- All-cause and UC-related hospitalization and surgery rates during Weeks 0 – 8.
- All cause and UC-related hospitalization and surgery rates during Weeks 8 – 52.
- Change from Baseline in fecal calprotectin over time.
- Time to achievement of remission (per Partial Mayo score).
- Time to achievement of response (per Partial Mayo score).
- Time to loss of response and factors associated with loss of response.
- Change from Baseline in histologic score at Week 8.
- Change from Baseline in histologic score at Week 52.
- Proportion of subjects achieving clinical remission per Full Mayo score (defined as Full Mayo score, excluding the PGA subscore, ≤ 2 with no subscore > 1) at Week 8.
- Proportion of Week 8 responders (per Full Mayo score) achieving clinical remission (per Full Mayo score, excluding the PGA subscore) at Week 52.
- Change in presence of extraintestinal manifestations over time.

Additional analyses are outlined in the protocol.

Criteria for Evaluation (Continued):

Pharmacokinetics:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline and Weeks 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits. Pre-dosing serum samples for HACAs and infliximab concentrations will be collected at Week 0.

Blood samples will be collected for the measurement of AAA just prior to dosing at Baseline and Weeks 4, 8, 12, 24, 37, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits.

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:

The following statistical analysis plan is for subjects recruited in the main study. A separate statistical analysis plan will be provided for subjects recruited in the Japan sub-study and for all the subjects recruited in the main study and the Japan sub-study (See Appendix K).

Efficacy:

The primary endpoint is the proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8 in the intent-to-treat (ITT) analysis set. The ITT analysis set includes all randomized subjects. The difference between the higher induction regimen arm versus the standard induction regimen arm in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use, and Baseline corticosteroid use. A CMH based two-sided 95% confidence interval for the difference between treatment arms will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 8 endpoint. Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non-responders for the Week 52 analyses. As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as IMM use at Baseline, Baseline CRP, and disease severity at Baseline will also be performed for the primary endpoint.

For CMH test statistic, if the condition of each stratum to have at least one subject with each treatment and at least one subject with each possible outcome is violated for the primary approach to the primary efficacy endpoint, the stratification factor Baseline corticosteroid use will be dropped from the CMH model in the analysis of all categorical variables.

Statistical Methods (Continued):

Efficacy (Continued):

The 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 an alpha level of 0.050 (two-sided) in ranked endpoint order until the significant level exceeds 0.05. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables. For Week 8 endpoints, the difference between the higher adalimumab induction arm versus the standard adalimumab induction arm will be assessed using ITT analysis set. For Week 52 endpoints, the difference between the eow arm versus the ew arm will be assessed using Intent-to-Treat maintenance (ITT-M) analysis set. The ITT-M analysis set includes all subjects who were re-randomized at Week 8. Categorical data will be described by frequency and percentage; continuous data will be described by mean, standard deviation, minimum, median, and maximum. In general, the secondary endpoints at Week 8 that are of the binary type will be analyzed using a two-sided CMH test adjusted for previous infliximab use and Baseline corticosteroid use in the ITT analysis set, and the secondary endpoints at Week 52 that are of the binary type will be analyzed using a two-sided CMH test adjusted for induction treatment regimen, and remitter status (per Full Mayo score) at Week 8 (where applicable) in the ITT-M analysis set. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. Continuous secondary efficacy variables will be analyzed using Analysis of Covariance (ANCOVA) with factor for treatment arm, stratification variables and Baseline values. NRI for missing data will be used for categorical endpoints. Procedures for handling missing data for continuous endpoints will be described in the Statistical Analysis Plan.

Pharmacokinetic:

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

Immunogenicity:

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

Statistical Methods (Continued):

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 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 medication and within 70 days after the last dose of the study medication. Treatment-emergent AEs will be summarized separately for the double-blind induction period (Week 0 to Week 8), double-blind maintenance period (Week 8 to 70 days after the last dose of the study medication), and Study M14-033 (Week 0 to 70 days after the last dose of the study medication). An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to PD (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. Other safety variables like laboratory data will be described by descriptive statistics. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

Has been changed to read:

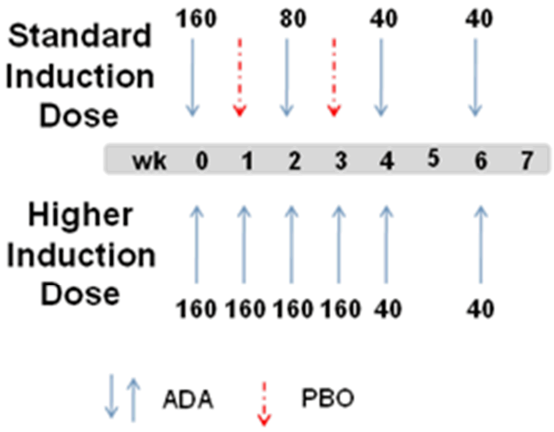
AbbVie Inc.	**Protocol Number:** M14-033
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 16 June 2016
Protocol Title: A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis	
Objective: The objective is to evaluate safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active Ulcerative Colitis (UC).	
Investigators: Multicenter Trial (Investigator information on file at AbbVie).	
Study Sites: Approximately 125 sites for the main study and approximately 21 sites for the Japan sub-study.	
Study Population: Male and female subjects ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active UC (up to 25% infliximab-experienced).	
Number of Subjects to be Enrolled: For the main Induction Study, approximately 840 subjects (504 subjects in the higher induction dose regimen and 336 subjects in the standard induction dose regimen) will be enrolled at approximately 125 sites worldwide. All subjects who complete the Induction Study (regardless of achievement of response at Week 8) will continue into the Maintenance Study. An additional 100 Japanese subjects (60 in the higher induction dose regimen and 40 in the standard induction dose regimen) in a Japan sub-study will be enrolled at 21 Japan sites. In both the main study and Japan sub study, up to 25% of subjects with previous infliximab exposure may be enrolled.	
Methodology: This Phase 3 study design includes the Screening Period followed by an 8-Week double blind Induction Study and a 44-Week double blind Maintenance Study. The Induction Study: will evaluate the efficacy and safety of a higher induction dosing regimen of adalimumab versus standard induction dosing in inducing clinical remission at Week 8 in subjects with moderately to severely active UC. The Maintenance Study: will evaluate the safety and efficacy of 44 weeks of three maintenance dosing regimens of adalimumab in achieving clinical remission at Week 52 (from the Induction Study Baseline) in subjects with moderately to severely active UC who achieved clinical response at Week 8 of the Induction Study.	

Methodology (Continued):

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 8 will represent the final assessment in the Induction Study. Week 52 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study). Subjects will have moderately to severely active UC as defined by a Mayo Score of 6 to 12 points with an endoscopy subscore of 2 or 3, confirmed by a central reader. For all Mayo Score evaluations throughout the entire study, the stool frequency and the rectal bleeding subscores will be calculated based on entries recorded into the subject's diary.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the Induction Study. During the Induction Study, subjects will be randomized at Baseline to one of 2 double-blinded adalimumab induction regimens (higher dose or standard dose) in a 3:2 ratio, as shown in the following figure. Use of the 3:2 randomization scheme allows for collection of additional safety data with the higher induction dose regimen. The randomization will be stratified by previous infliximab use and Baseline corticosteroid use.

8-Week Double-Blind Induction Study



The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6 leads to a total adalimumab dose over 8 weeks that is approximately twice that of the standard induction dose regimen (720 mg versus 320 mg). The higher induction dose regimen was designed for rapid attainment of higher adalimumab serum concentrations in order to rapidly control inflammation. Pre dosing serum samples for infliximab concentration and human antichimeric antibodies (HACAs) will be collected at Week 0. Pre-dosing serum samples for adalimumab drug levels will be collected at Weeks 0, 2, 4, and 8. Pre-dosing serum samples for anti-adalimumab antibodies will be collected at Weeks 0, 4, and 8.

Methodology (Continued):

At Week 4, all subjects who are taking oral corticosteroids from Baseline will have their corticosteroid therapy tapered according to the proposed tapering schedule specified in the 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.

At the conclusion of the 8-Week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study. Re-randomization into the Maintenance Study will be stratified by induction treatment regimen in the Induction Study and response status (per Full Mayo Score) at Week 8. Among the responders at Week 8, the re-randomization will be further stratified by remission status (per Full Mayo score) at Week 8. All subjects in the main study who complete the Induction Study) will be re-randomized into one of three blinded treatment groups in a 2:2:1 ratio:

- Adalimumab 40 mg every other week (eow)
- Adalimumab 40 mg every week (ew)
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory)*

* 1) All subjects in the TDM dosing regimen will receive 40 mg eow at Week 8 and Week 10. At Weeks 12, 24, and 37, the regimen will be adjusted for subjects meeting the dose adjustment criteria (see table below) based on blinded serum concentrations at the prior visit (Weeks 10, 22 and 35, respectively) and rectal bleeding subscore at the prior and current visits as follows:

- Subjects receiving 40 mg eow who meet the dose adjustment criteria will escalate to 40 mg weekly.
- Subjects receiving 40 mg ew who meet the dose adjustment criteria will receive a one-time dose of 160 mg at the visit, and resume 40 mg ew starting the following week.

2) Japan sub-study does not have TDM dosing regimen. Subjects will be re-randomized into Adalimumab 40 mg eow treatment group or Adalimumab 40 mg ew treatment group in a 1:1 ratio.

Pre-dosing serum samples for adalimumab drug levels will be collected in all subjects at Weeks 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52/Premature Discontinuation (PD), and unscheduled visits. Pre-dosing serum samples for anti-adalimumab antibodies will be collected at Weeks 12, 24, 37, 52/PD, and unscheduled visits.

The goal of the TDM dosing regimen is to attain serum adalimumab levels within a targeted concentration range (selected based on exposure-response analyses from Study M06-827) while avoiding excessively high concentrations. During maintenance therapy in Study M06-827, concentrations ranged from 0 to 39.3 µg/mL with eow dosing and 0 to 38.0 µg/mL with ew dosing. The lower bound (10 µg/mL) of the targeted concentration range for the TDM dosing regimen is similar to the median concentrations observed over time for the subjects in remission at Week 52 of Study M06-827 (11.4, 10.6, and 10.8 µg/mL, for Weeks 8, 32, and 52, respectively). Use of this concentration as the minimum threshold to trigger dose escalation will lead to the majority of subjects achieving concentrations greater than 10 µg/mL. Since serum adalimumab concentrations roughly double with a doubling of dose, an upper bound of 20 µg/mL is expected to achieve maximal trough concentrations in the range of the highest trough concentrations observed in Study M06-827. It is expected that approximately 60% of subjects in the TDM dosing regimen will escalate to ew dosing and 15% or fewer will receive reinduction using this concentration range plus the Rectal Bleeding Subscore (RBS) criteria outlined in the table below as a guide to adjust adalimumab dosing.

Methodology (Continued):

TDM Dose Adjustment Criteria[a]

Adalimumab Serum Concentration[b]	Rectal Bleeding Subscore[c]	Dose Escalate?[d]
< 10 µg/mL	Any	Yes
10 µg/ml to 20 µg/mL	< 1	No
10 µg/ml to 20 µg/mL	≥ 1	Yes
> 20 µg/mL	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. The score entries into the subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding Subscore for each study visit.

d. For subjects on 40 mg eow, escalate to 40 mg ew. Subjects on 40 mg ew will receive "reinduction" with a dose of 160 mg at the visit and resume 40 mg ew 1 week later.

Note: There will be no allowance for dose adjustment in the adalimumab eow or ew dosing regimens.

Study visits for clinical and safety assessments will be performed at Baseline (Week 0), Weeks 1, 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, and 52/PD. All subjects will be provided with a Subject Diary where they will record ulcerative colitis-related symptoms (daily stool frequency, abdominal discomfort, number of bloody stools, fecal urgency, and general well-being), use of anti-diarrheals, use of medications for endoscopy preparation, and study drug dosing information throughout the study. Blood samples will be collected for hs-CRP, adalimumab serum concentrations, anti-adalimumab antibody (AAA) levels, and other biomarker analyses. In addition, stool samples for calprotectin and microbiota metagenomic analyses will be collected. The stool samples should be taken before starting bowel preparations for endoscopy. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy for histologic assessment during Screening, at Week 8 and at Week 52/PD (for subjects who remain in the study through at least Week 24) with local investigator assessment for Mayo endoscopic subscore confirmed by a central reader. The central reviewer scoring will be used for all efficacy assessments. The endoscopy subscore result from the central reviewer during the screening period will be used to evaluate the eligibility of a subject to enroll in the study.

Subjects who consent to participate in the optional pharmacogenetic (PG) analysis should have an additional blood sample drawn at Baseline and at Week 52/PD. If the sample is not collected at Baseline, preferably it should be collected at the next study visit.

Subjects will be discontinued if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator. Subjects experiencing an active infection or those for whom the investigator feels dose escalation is not advisable should contact the Study Designated Physician.

Methodology (Continued):

Subjects will only be allowed to change the dosage of UC-specific concomitant medications as specified below:

- At Week 4, all subjects who are taking oral corticosteroids from Baseline will have their corticosteroid therapy tapered according to the proposed tapering schedule specified in the Protocol. 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.
- 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.

Subjects in whom UC-related medications (defined as oral or rectal aminosalicylates, systemic or rectal corticosteroids, or systemic medications affecting the immune system, including thiopurines, MTX, and agents listed in the study exclusion criteria) 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.

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

Diagnosis and Main Criteria for Inclusion/Exclusion:

The following Inclusion/Exclusion criteria are for subjects enrolled in the main study. Separate Inclusion/Exclusion criteria for subjects recruited in Japan will be followed in the Japan sub-study.

Main Inclusion:

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
2. Male or female ≥ 18 and ≤ 75 years of age at the Baseline visit.
3. Subject with a diagnosis of UC for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period, with exclusion of current infection, dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.

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

Main Inclusion (Continued):

4. Active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) 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 or immunosuppressants as defined below):
   - Subject taking oral corticosteroids, excluding budesonide or beclomethasone:
     - Oral corticosteroid dose must be ≤ 40 mg/day (prednisone or equivalent);
       - For subject 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 subject 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 subject 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 subject 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.
   - Subject taking oral beclomethasone:
     - Dose must not exceed 5 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.

   or,
   - At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP) or injectable methotrexate (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 dosing and duration of use criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline), however prior or current 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.

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

Main Inclusion (Continued):

5. Subject may be included if they have previously experienced a benefit for their UC from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of UC related symptoms) or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss of response or lack of tolerability will be required.
6. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly 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);
   - A 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.
7. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.
8. Subject has a negative tuberculosis (TB) Screening Assessment. If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline.
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, chest x-ray, 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 diagnosis and/or history of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. Received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to the Screening endoscopy and during the remainder of the Screening Period.
5. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
6. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
7. Positive pregnancy test at Screening (serum) or Baseline (urine).
8. Female who is breast-feeding or considering becoming pregnant during the study.

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

Main Exclusion (Continued):

9. History of clinically significant drug or alcohol abuse in the last 12 months.
10. Subject on azathioprine, 6-MP, 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.
11. Subject on oral aminosalicylates who:
    - Has not been on stable doses of these medications for at least 14 days prior to Baseline; or
    - Has discontinued use of aminosalicylates within 14 days of Baseline.
12. Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subject on oral budesonide > 9 mg/day; or subject on oral beclomethasone > 5 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 of at least 14 days in duration 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 oral 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 of at least 14 days in duration 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 has **not** been a current steroid course of at least 14 days in duration prior to Baseline; or
    - Subject taking oral beclomethasone:
      - has **not** been on a stable dose for at least 7 days prior to Baseline; or
      - but has **not** been on a current steroid course of at least 14 days in duration prior to Baseline; or

    Has been taking both oral budesonide (or oral beclomethasone) and oral prednisone (or equivalent) simultaneously

    and/or

    Has discontinued use of corticosteroids within 14 days of Baseline.
13. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
14. Positive Clostridium difficile *(C. difficile)* toxin stool assay during the Screening Period.
15. Currently receiving total parenteral nutrition (TPN).

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

Main Exclusion (Continued):

16. Subject who received any investigational agent or procedure (including previous fecal microbial transplantation) within 30 days or 5 half-lives prior to Week 0 (Baseline), whichever is longer.
17. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
18. 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.
19. 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®]) or previous participation in an adalimumab clinical study. Prior exposure to any anti-tumor necrosis factor (TNF) agent other than infliximab (including but not limited to adalimumab [Humira®], etanercept [Enbrel®], golimumab [Simponi®] or certolizumab pegol [Cimzia®]). Prior exposure to ustekinumab (Stelara®), tofacitinib (Xeljanz®) or vedolizumab (Entyvio®).
20. Subject with known hypersensitivity to the excipients of adalimumab (see Protocol).
21. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
22. 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. If the Screening endoscopy shows evidence of current dysplasia or malignancy, subject may not be enrolled in the study.
23. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).
24. Subject with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
25. 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.

26. Chronic recurring infections or active TB.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** 27. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and/or any other condition which would put the subject at risk by participation in the study. 28. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study. 29. 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.	
Investigational Products:	Adalimumab
Induction Study: **Double-Blind Induction Doses:** NOTE: In order to retain blinding, all subjects in the Standard Induction Dose Regimen will receive matching placebo injections in addition to the adalimumab injection at Weeks 1, 2 and 3.	Subjects will be randomized to receive one of 2 double-blind adalimumab induction dosing regimens. Standard Induction Dose Regimen: 160 mg at Week 0 and matching placebo at Week 1. Subjects will receive 80 mg at Week 2 and matching placebo at Week 3. Subjects will receive 40 mg at Week 4 and Week 6. Higher Induction Dose Regimen: 160 mg at Weeks 0, 1, 2, and 3. Subjects will receive 40 mg at Week 4 and Week 6.

Maintenance Study: **Double-Blind Maintenance Doses:**	Subjects will be re-randomized to receive one of 3 double-blind adalimumab maintenance dosing regimens. Adalimumab 40 mg eow Regimen: 40 mg every other week, starting at Week 8 until Week 50. Matching Placebo will be administered every other week, starting at Week 9 until Week 51. No dose will be administered at Week 52. Adalimumab 40 mg ew Regimen: 40 mg every week, starting at Week 8 until Week 51. No dose will be administered at Week 52. Adalimumab TDM Regimen: 40 mg eow at Week 8 and Week 10. Matching placebo at Week 9 and Week 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria. Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly. Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week. Subjects receiving 40 mg eow who do not meet the regimen adjustment criteria will receive adalimumab 40 mg eow and placebo at alternative weeks. No dose will be administered at Week 52. NOTE: In order to retain blinding, all subjects in the 40 mg eow and 40 mg ew regimen groups and subjects who do not meet the criteria for dose escalation in the TDM regimen group will receive matching placebo injections in addition to the adalimumab injection (placebo reinduction) at Weeks 24 and 37.
Mode of Administration:	Subcutaneous injection (SC)

Duration of Treatment: The overall study treatment duration is 52 weeks (8 weeks of induction therapy during the Induction Study followed by 44 weeks of maintenance therapy during the Maintenance Study). There will be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely. The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

Criteria for Evaluation:

The following analysis is for subjects recruited in the main study. A separate statistical analysis will be performed for subjects recruited in the Japan sub-study and for all subjects recruited in the main study and the Japan sub-study.

Efficacy:

For the Induction Study endpoints, the subjects receiving the higher adalimumab induction dose regimen will be compared to subjects receiving the standard adalimumab induction dose regimen. For the Maintenance Study endpoints, the subjects receiving the eow regimen will be compared to subjects receiving the ew regimen. The TDM regimen will be used for exploratory analyses. For the primary endpoints, clinical remission or response will be evaluated using Full Mayo Score. Exploratory analysis will also be performed using Full Mayo Score excluding PGA (Adapted Mayo Score) and Full Mayo Score excluding Endoscopy Subscore (Partial Mayo Score).

Criteria for Evaluation (Continued):

Efficacy (Continued):

The primary efficacy endpoint for the Induction Study is:

- Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

- Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Induction Study are:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.
2. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.
3. Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 8.
4. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.
5. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.

Additional pre-specified endpoints in the Induction Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Induction Study
- All-cause and UC-related hospitalization and surgery rates during Weeks 0 – 8.
- Change from Baseline in histologic score at Week 8.
- Proportion of subjects achieving clinical remission per Adapted Mayo Score (defined as stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1) at Week 8.
- Proportion of subjects achieving Full Mayo score, excluding the PGA subscore, ≤ 2 with no subscore > 1 at Week 8.
- Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 8.
- Relationship between histologic scores and endoscopic subscore of 0 at Week 8.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Maintenance Study are:

1. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
2. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 90 days at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
4. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.

Criteria for Evaluation (Continued):

Efficacy (Continued):

5. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
7. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
8. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 52.
9. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
10. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
11. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
12. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

Additional pre-specified endpoints in the Maintenance Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Maintenance Study by Week 8 response status.
- Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic improvement at Week 52.
- All cause and UC-related hospitalization and surgery rates during Weeks 8 – 52.
- Change from Baseline in histologic score at Week 52.
- Proportion of Week 8 responders per Adapted Mayo Score (defined as decrease from Baseline in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1) achieving clinical remission per Adapted Mayo Scores at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) achieving Full Mayo score, excluding the PGA subscore, ≤ 2 with no subscore > 1 at Week 52.
- Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 52.
- Relationship between histologic scores and endoscopic subscore of 0 at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.

Criteria for Evaluation (Continued):

Efficacy (Continued):

The following additional pre-specified endpoints will also be analyzed in both the Induction Study and the Maintenance Study.

- Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.
- Proportion of subjects who are taking corticosteroids at Baseline and are steroid-free over time.
- Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.
- Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score ≤ 2 with no subscore > 1) score over time.
- Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of ≥ 2 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) over time.
- Change from Baseline in hs-CRP over time.
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in IBDQ score over time.
- Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.
- Change from Baseline in SF-36 score over time.
- Change from Baseline in fecal calprotectin over time.
- Time to achievement of remission (per Partial Mayo score).
- Time to achievement of response (per Partial Mayo score).
- Time to loss of response and factors associated with loss of response.
- Change in presence of extraintestinal manifestations over time.

Pharmacokinetics:

Blood samples will be collected for the measurement of serum adalimumab concentrations just prior to dosing at Baseline and Weeks 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits. Pre-dosing serum samples for HACAs and infliximab concentrations will be collected at Week 0.

Blood samples will be collected for the measurement of AAA just prior to dosing at Baseline and Weeks 4, 8, 12, 24, 37, 52 (or at the PD visit if the subject discontinues prior to Week 52), and unscheduled visits.

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:

The following statistical analysis plan is for subjects recruited in the main study. A separate statistical analysis plan will be provided for subjects recruited in the Japan sub-study and for all the subjects recruited in the main study and the Japan sub-study (See Appendix K).

Efficacy:

For the Induction Study, a total of 840 subjects will be allocated to the adalimumab higher induction dosing regimen and the adalimumab standard induction dosing regimen in a 3:2 ratio (504 and 336 subjects in each regimen, respectively). The sample size for the Induction Study is based on the expected proportions of subjects who achieve clinical remission at Week 8. Assuming the clinical remission rate of 35% in the adalimumab higher induction dosing regimen and 20% in the adalimumab standard induction dosing regimen at Week 8, this sample size will provide > 95% power to detect a difference of 15% between the two treatment groups for the primary endpoint of the Induction Study using two-sided Fisher's Exact test at a 0.05 significance level. The efficacy analysis will be based on intent-to-treat analysis set. The intent-to-treat analysis set includes all randomized subjects who receive at least one dose of study drug in the Induction Study 1 (ITT1). The difference between the higher induction dosing regimen group versus the standard induction dosing regimen group in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 8 endpoint. Subjects with missing Mayo score data at Week 8 will be classified as Week 8 non-responders for the Week 52 Maintenance Study analyses. As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint.

For the Maintenance Study, the sample size is based on the expected proportions of subjects who achieve clinical remission at Week 52. Assuming the average response rate at Week 8 in the Induction Study is 50%, a total of 420 Week 8 responders will be re-randomized to adalimumab 40 mg eow, adalimumab 40 mg ew, and TDM regimen in a ratio of 2:2:1; i.e., 168 subjects each in the eow and ew groups and 84 subjects in the TDM regimen. Assuming the Week 52 clinical remission rate of 48% in the ew group and 30% in the eow group among Week 8 responders, this sample size will provide 90% power to detect a treatment difference of 18% between the two groups using two-sided Fisher's Exact test at a 0.05 significance level. The efficacy analysis will be based on intent-to-treat analysis set. The intent-to-treat analysis set includes all re-randomized subjects who receive at least one dose of study drug in the Maintenance Study (ITT2). The difference between the adalimumab eow regimen versus the adalimumab ew regimen in the proportion of subjects achieving clinical remission at Week 52 among Week 8 responders will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for the induction treatment regimen dosing and remitter status at Week 8 (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site). A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 52 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 52 endpoint.

Statistical Methods (Continued):

Efficacy (Continued):

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint.

The secondary efficacy variables of the Induction Study and the Maintenance Study are divided into two groups. The first group includes ranked secondary endpoints, which are ranked by clinical importance. Statistical significance is assessed at an alpha level of 0.050 (two-sided) in ranked endpoint order until the significant level exceeds 0.05. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables. For the Induction Study Week 8 endpoints, the difference between the higher adalimumab induction dosing regimen versus the standard adalimumab induction dosing regimen will be assessed using ITT1 analysis set. For the Maintenance Study Week 52 endpoints, the difference between the eow group versus the ew group will be assessed using ITT2 analysis set. Categorical data will be described by frequency and percentage; continuous data will be described by mean, standard deviation, minimum, median, and maximum. In general, the secondary endpoints at Week 8 for the Induction Study that are of the binary type will be analyzed using a two-sided CMH test adjusted for previous infliximab use and Baseline corticosteroid use using the ITT1 analysis set, and the secondary endpoints at Week 52 for the Maintenance Study that are of the binary type will be analyzed using a two-sided CMH test adjusted for induction treatment regimen and remitter status (per Full Mayo score) at Week 8 (where applicable) using the ITT2 analysis set. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. Continuous secondary efficacy variables will be analyzed using Analysis of Covariance (ANCOVA) with factor for treatment group, stratification variables and Baseline values. NRI for missing data will be used for categorical endpoints. Procedures for handling missing data for continuous endpoints will be described in the Statistical Analysis Plan.

Pharmacokinetic:

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

Immunogenicity:

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

Safety:

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed for both Induction and Maintenance Studies using the safety analysis set, which includes all subjects who receive at least one dose of study medication in each Study, respectively. Treatment-emergent adverse events will be tabulated by system organ class and by MedDRA preferred term by treatment group for the Induction Study and the Maintenance Study, and for any adalimumab over the entire study. Mean changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
"I-TT," "ITT-M," "ITT," "ITT-M," "J-ITT" and "J-ITT-M" previously read:

I-ITT	Integrated Intent-To-Treat
I-ITT-M	Integrated Intent-To Treat Maintenance
ITT	Intent-To-Treat
ITT-M	Intent-to-Treat Maintenance
J-ITT	Japan Integrated Intent-To-Treat
J-ITT-M	Japan Integrated Intent-To-Treat Maintenance

Has been changed to read:

I-ITT1	Integrated Intent-To-Treat Induction Study
I-ITT2	Integrated Intent-To Treat Maintenance Study
ITT1	Intent-To-Treat Induction Study
ITT2	Intent-to-Treat Maintenance Study
J-ITT1	Japan Integrated Intent-To-Treat Induction Study
J-ITT2	Japan Integrated Intent-To-Treat Maintenance Study

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add: "PGA, "PMS" and "SFS"

PGA	Physician's Global Assessment
PMS	Partial Mayo Score
SFS	Stool Frequency Subscore

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Definition of Terms
Add: "Adapted Mayo Score," "Remission per Adapted Mayo Score" and "Response per Adapted Mayo Score"

Adapted Mayo Score	Full Mayo Score minus the Physician's Global Assessment (PGA)
Remission per Adapted Mayo Score	An Adapted Mayo Score ≤ 2, with stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1
Response per Adapted Mayo Score	A decrease in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1

Section 3.0 Introduction
Seventh paragraph, first sentence previously read:

The purpose of this study is to evaluate a higher induction and maintenance regimen, including an exploratory arm evaluating a therapeutic drug monitoring strategy, than the standard approved adalimumab induction regimen (160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every other week [eow] beginning at Week 4) for induction and maintenance therapy in adult patients with moderately to severely active ulcerative colitis.

Has been changed to read:

The purpose of this study is to evaluate a higher induction and maintenance regimen, including an exploratory dosing regimen evaluating a therapeutic drug monitoring strategy, than the standard approved adalimumab induction regimen (160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every other week [eow] beginning at Week 4) for induction and maintenance therapy in adult patients with moderately to severely active ulcerative colitis.

Section 3.0 Introduction
Last paragraph
Add: new second sentence

Both the main study and Japan sub-study include an Induction Study and a Maintenance Study.

Section 3.1 Differences Statement
First paragraph previously read:

The differences between Study M14-033 and the other UC studies (Study M06-826 and Study M06-827), are the inclusion of a higher induction dose, a higher maintenance dose (weekly dosing) and an adjustable dosing arm based on therapeutic drug monitoring during the maintenance phase, which will allow for a greater range of exposure and ultimately provide greater precision around adalimumab dosing/exposure and efficacy/safety relationships in subjects with moderately to severely active ulcerative colitis. The pharmacokinetic profile of adalimumab during induction and maintenance phases and its relationship to efficacy in adult subjects with moderately to severely active ulcerative colitis will be characterized.

Has been changed to read:

The differences between Study M14-033 and the other UC studies (Study M06-826 and Study M06-827), are the inclusion of a higher induction dose, a higher maintenance dose (weekly dosing) and an adjustable dosing regimen based on therapeutic drug monitoring during the Maintenance Study, which will allow for a greater range of exposure and ultimately provide greater precision around adalimumab dosing/exposure and efficacy/safety relationships in subjects with moderately to severely active ulcerative colitis. The pharmacokinetic profile of adalimumab during Induction and Maintenance Studies and its relationship to efficacy in adult subjects with moderately to severely active ulcerative colitis will be characterized.

Section 4.0 Study Objective
Previously read:

The primary study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis.

Has been changed to read:

The study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis.

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

The study was designed to enroll 525 subjects in the main study (315 in the higher induction dose regimen and 210 in the standard induction dose regimen) at approximately 125 sites worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. There also will be 80 Japanese subjects (48 in the higher induction dose regimen and 32 in the standard induction dose regimen) in a Japan sub-study to be enrolled at 21 Japan sites.

Has been changed to read:

The study was designed to enroll 840 subjects in the main study (504 subjects in the higher induction dose regimen and 336 subjects in the standard induction dose regimen) at approximately 125 sites worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. There also will be 100 Japanese subjects (60 subjects in the higher induction dose regimen and 40 subjects in the standard induction dose regimen) in a Japan sub-study to be enrolled at 21 Japan sites.

Section 5.1 Overall Study Design and Plan: Description
Third paragraph, second and third bullet previously read:

- An 8-Week Double-Blind Induction Period
- A 44-Week Double-Blind Maintenance Period

Has been changed to read:

- An 8-Week Double-Blind Induction Study
- A 44-Week Double-Blind Maintenance Study

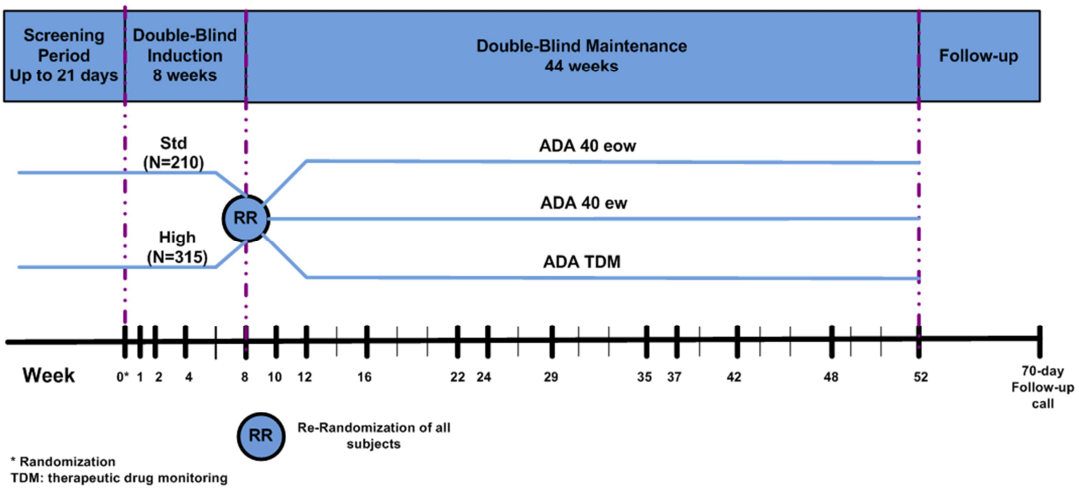
Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph
Add: new first, second, third and fourth sentence

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 8 will represent the final assessment in the Induction Study and the beginning of the Maintenance Study. Week 52 will represent the final assessment in the Maintenance Study (representing 44 weeks of maintenance treatment in the Maintenance Study).

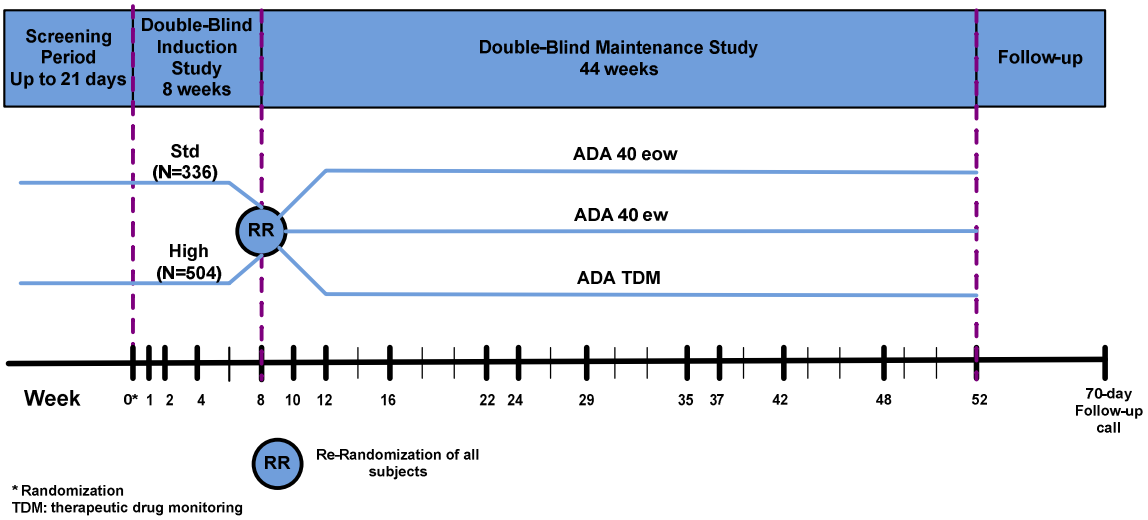
Section 5.1 Overall Study Design and Plan: Description
Fifth paragraph
Add: new last sentence

If the sample is not collected at Baseline, it should be collected at the next study visit.

Figure 1. Study Schematic
Previously read:



Has been changed to read:



Section 5.1 Overall Study Design and Plan: Description
Subsection Screening Period
Second paragraph, first and second sentence previously read:

Subjects who meet all eligibility criteria during the Screening Period (refer to Section 5.2.1) will enter the 8-Week Double-Blind Induction Period. The length of time between screening and the 8-Week Double-Blind Induction Period Baseline Visit must allow time for endoscopy central reading and lab results.

Has been changed to read:

Subjects who meet all eligibility criteria during the Screening Period (refer to Section 5.2.1) will enter the 8-Week Double-Blind Induction Study. The length of time between screening and the 8-Week Double-Blind Induction Study Baseline Visit must allow time for endoscopy central reading and lab results.

Section 5.1 Overall Study Design and Plan: Description
Subsection 8-Week Double-Blind Induction Period
Subsection title previously read:

8-Week Double-Blind Induction Period

Has been changed to read:

8-Week Double-Blind Induction Study

Section 5.1 Overall Study Design and Plan: Description
Subsection 8-Week Double-Blind Induction Period
First paragraph, first sentence previously read:

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the 8-Week Induction Period.

Has been changed to read:

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the 8-Week Induction Study.

Figure 2. 8-Week Double-Blind Induction Period
Figure title previously read:

8-Week Double-Blind Induction Period

Has been changed to read:

8-Week Double-Blind Induction Study

Section 5.1 Overall Study Design and Plan: Description
Subsection <u>8-Week Double-Blind Induction Period</u>
Last paragraph, first sentence previously read:

At Week 4, all subjects who are on oral steroids will have their steroid dose tapered according to the proposed tapering schedule outlined in the protocol.

Has been changed to read:

At Week 4, all subjects who are on oral corticosteroids from Baseline will have their corticosteroid dose tapered according to the proposed tapering schedule outlined in the protocol.

Section 5.1 Overall Study Design and Plan: Description
Subsection <u>44-Week Double-Blind Maintenance Period</u>
Subsection title and text previously read:

<u>44-Week Double-Blind Maintenance Period</u>

At the conclusion of the 8-Week Double-Blind Induction Period, subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Period to one of three treatment arms in a 2:2:1 ratio:

- Adalimumab 40 mg eow
- Adalimumab 40 mg every week (ew)
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory arm). See Figure 3. (The Japan sub-study does not have a TDM arm. Subjects will

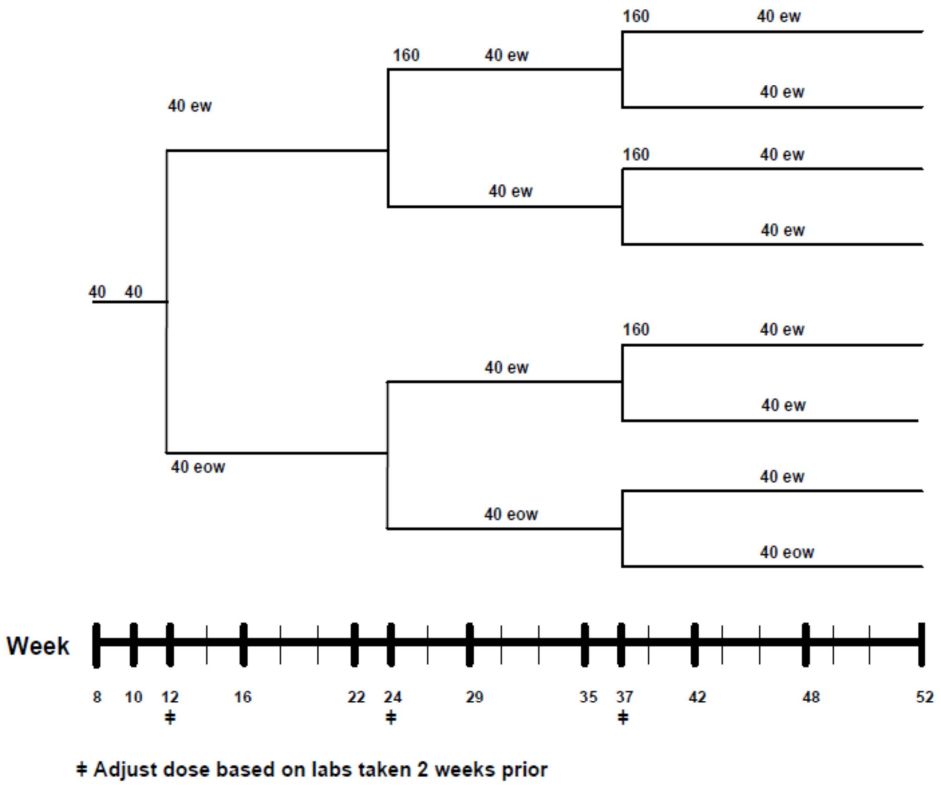
be randomized into Adalimumab 40 mg eow arm or Adalimumab 40 mg ew in a 1:1 ratio.)

At Week 8, subjects will be re-stratified by:

- Induction treatment regimen

  and
- Response status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. Among the responders at Week 8, the randomization will be further stratified by remission status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) determined at Week 8.

Figure 3. Drug Monitoring (TDM) Regimen



Subjects in the adalimumab 40 mg eow arm will continue to receive 40 mg eow until the end of the study. Subjects in the adalimumab 40 mg ew arm will start 40 mg ew at Week 8 until the end of the study.

All subjects in the TDM arm will receive 40 mg eow at Week 8 and Week 10, and may have their adalimumab dose adjusted at Weeks 12, 24, and 37 based on criteria assessing blinded serum concentration at the prior visit (Weeks 10, 22, and 35, respectively, Table 1) and rectal bleeding subscore (RBS) at the prior and current visits as follows:

- Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly.
- Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week.

Table 1. TDM Arm Dose Adjustment Criteria

TDM Arm Dose Adjustment Criteria[a]		
Adalimumab Serum Concentration[b]	**Rectal Bleeding Subscore[c]**	**Dose Escalate?[d]**
< 10 µg/mL	Any	Yes
10 µg/mL to 20 µg/mL	< 1	No
10 µg/mL to 20 µg/mL	≥ 1	Yes
> 20 µg/mL	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 SDP.

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

c. The score entries into the subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit, Appendix C.

d. For subjects on 40 mg eow, escalate to 40 mg ew. Subjects on 40 mg ew will receive "reinduction" with a dose of 160 mg at the visit and resume 40 mg ew 1 week later.

Note: There will be no allowance for dose adjustment in the adalimumab eow or ew dosing arms.

Throughout the study, subjects will only be allowed to change the dosage of UC-specific concomitant medications as specified in Section 5.2.3.2.

Subjects will return to the study site at scheduled visits and complete study procedures for each visit as outlined in Section 5.3.1.1. Site staff to ensure all data needed to complete Weeks 12, 24 and 37 is available prior to the subject arriving at the site. Notify the Clinical Research Associate (CRA) should any needed reports be missing. No study drug will be administered or injected at the final visit.

Has been changed to read:

44-Week Double-Blind Maintenance Study

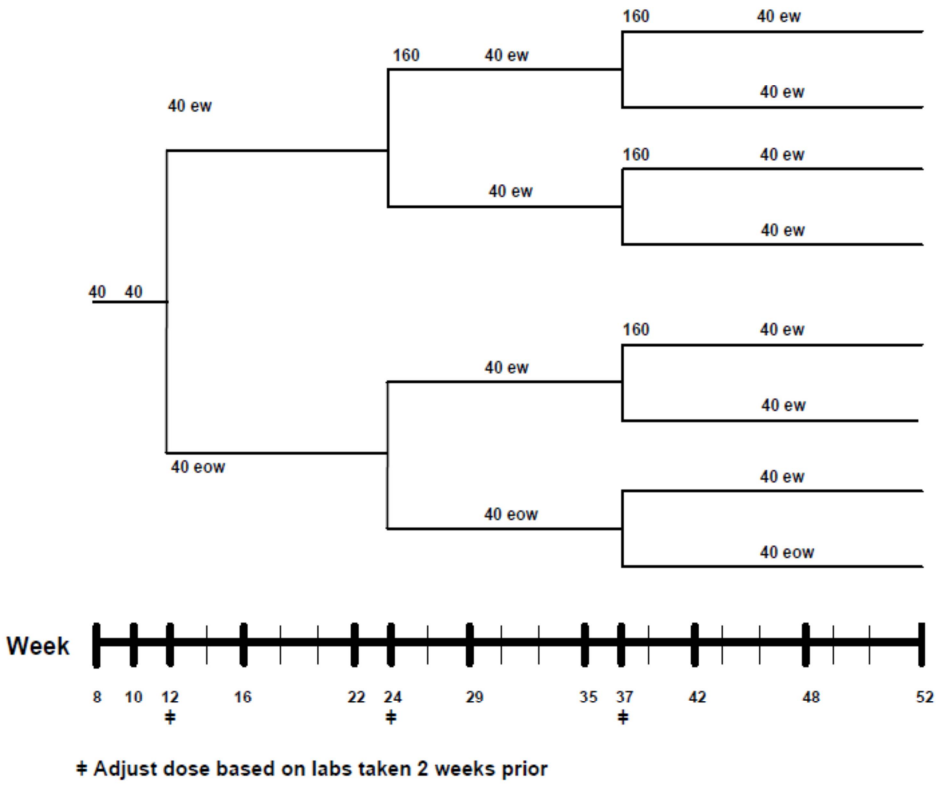
At the conclusion of the 8-Week Double-Blind Induction Study, subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Study to one of three treatment groups in a 2:2:1 ratio:

- Adalimumab 40 mg eow
- Adalimumab 40 mg every week (ew)
- Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory). See Figure 3. (The Japan sub-study does not have a TDM regimen. Subjects will be randomized into Adalimumab 40 mg eow treatment group or Adalimumab 40 mg ew treatment group in a 1:1 ratio.)

At Week 8, subjects will be re-stratified by:

- Treatment regimen in the Induction Study
  and
- Response status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. Among the responders at Week 8, the re-randomization will be further stratified by remission status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) determined at Week 8.

Figure 3. Drug Monitoring (TDM) Regimen



Subjects in the adalimumab 40 mg eow treatment group will continue to receive 40 mg eow until the end of the study. Subjects in the adalimumab 40 mg ew treatment group will start 40 mg ew at Week 8 until the end of the study.

All subjects in the TDM regimen will receive 40 mg eow at Week 8 and Week 10, and may have their adalimumab dose adjusted at Weeks 12, 24, and 37 based on criteria assessing blinded adalimumab serum concentration at the prior visit (Weeks 10, 22, and 35, respectively, Table 1) and rectal bleeding subscore (RBS) at the prior and current visits as follows:

- Subjects receiving 40 mg eow and meeting the regimen adjustment criteria will escalate to 40 mg weekly.

- Subjects receiving 40 mg ew and meeting the regimen adjustment criteria will receive a one-time dose of 160 mg at the visit, followed by 40 mg ew starting the following week.

Table 1. TDM Dose Adjustment Criteria

TDM Dose Adjustment Criteria[a]		
Adalimumab Serum Concentration[b]	**Rectal Bleeding Subscore[c]**	**Dose Escalate?[d]**
< 10 µg/mL	Any	Yes
10 µg/mL to 20 µg/mL	< 1	No
10 µg/mL to 20 µg/mL	≥ 1	Yes
> 20 µg/mL	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 SDP.

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

c. The score entries into the subject's diary based on 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit, Appendix C.

d. For subjects on 40 mg eow, escalate to 40 mg ew. Subjects on 40 mg ew will receive "reinduction" with a dose of 160 mg at the visit and resume 40 mg ew 1 week later.

Note: There will be no allowance for dose adjustment in the adalimumab eow or ew dosing groups.

Throughout the study, subjects will only be allowed to change the dosage of UC-specific concomitant medications as specified in Section 5.2.3.2.

Subjects will return to the study site at scheduled visits and complete study procedures for each visit as outlined in Section 5.3.1.1. Site staff to ensure all data needed to complete Weeks 12, 24 and 37 is available prior to the subject arriving at the site. Notify the Clinical Research Associate (CRA) should any needed reports be missing. No study drug will be administered or injected at the final visit.

Section 5.2 Selection of Study Population
First and second paragraph previously read:

Five hundred and twenty-five subjects will be enrolled at up to 125 non-Japan sites.

An additional 80 subjects will be enrolled at approximately 21 sites in Japan as part of a separate Japan sub-study outlined in Appendix K.

Has been changed to read:

Eight hundred and forty (840) subjects will be enrolled at up to 125 sites in the Main Study.

An additional 100 subjects will be enrolled at approximately 21 sites in Japan as part of a separate Japan sub-study outlined in Appendix K.

Section 5.2.2 Exclusion Criteria
Criterion 25 previously read:

25. Subjects with a positive result for 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 (+)

Has been changed to read:

25. Subjects with a positive result for 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.

Section 5.2.3.2 Concomitant Therapy
Third 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 through the end of the study.

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 Baseline values carried forward for non-categorical assessments) from that point forward.

Section 5.2.3.2 Concomitant Therapy
Fourth paragraph, first sentence previously read:

Subjects in whom the following UC-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 through the end of the study.

Has been changed to read:

Subjects in whom the following UC-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.

Table 2. Study Activities
Header row, column "8-Week Double-Blind Induction Period" and "44-Week Double-Blind Maintenance Period" previously read:

"8-Week Double-Blind Induction Period" and "44-Week Double-Blind Maintenance Period"

Has been changed to read:

"8-Week Double-Blind Induction Study" and "44-Week Double-Blind Maintenance Study"

Table 2. Study Activities
Table note "j."
Add: new last sentence

Further explanations of these tests are provided in the Laboratory Manual.

Table 2. Study Activities
Table note "m."
Add: new last sentence

Remaining sample will be stored for potential research testing.

Section 5.3.1.1 Study Procedures
Subsection <u>For the PPD Test:</u>
Ninth paragraph previously read:

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

Has been changed to read:

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 in medical history eCRF page.

Section 5.3.1.1 Study Procedures
Subsection <u>Hepatitis B Testing</u>
Previously read:

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 (+)

Has been changed to read:

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.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection <u>Collection of Samples for Adalimumab and AAA Assays</u>
Last paragraph, last sentence previously read:

The total number of samples planned (not including unscheduled visit sample collections) will not exceed 7,875 (15 samples × 525 subjects) for the adalimumab assay and 3,675 (7 samples × 525 subjects) for the AAA assay for the main study.

Has been changed to read:

The total number of samples planned (not including unscheduled visit sample collections) will not exceed 12,600 (15 samples × 840 subjects) for the adalimumab assay and 5,880 (7 samples × 840 subjects) for the AAA assay for the main study.

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

The total number of samples planned will not exceed 1050 (2 samples × 525 subjects) for the main study.

Has been changed to read:

The total number of samples planned will not exceed 1,680 (2 samples × 840 subjects) for the main study.

5.3.2.3 Disposition of Samples
Second sentence previously read:

Samples will be shipped pursuant to instructions from the onsite CRA.

Has been changed to read:

Samples will be shipped pursuant to instructions from the CRA.

Section 5.3.3.1 Primary Variable
Section title and text previously read:

5.3.3.1 Primary Variable

The primary efficacy variable is the proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

Has been changed to read:

5.3.3.1 Primary Variables

The primary efficacy variable for the Induction Study is the proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy variable for the Maintenance Study is the proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

Section 5.3.3.2 Secondary Variables
First paragraph and item list previously read:

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) include:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.
2. Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
4. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
5. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.
7. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
8. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.

9. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
10. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.
11. Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 8.
12. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 52.
13. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
14. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
15. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.
16. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.
17. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
18. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

Has been changed to read:

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Induction Study are:

1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.
2. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.

3. Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 8.
4. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.
5. Proportion of subjects achieving endoscopic subscore of 0 at Week 8.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Maintenance Study are:

1. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
2. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
4. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.
5. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
7. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
8. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ ≥ 16 from Baseline) at Week 52.

9. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
10. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
11. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
12. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.

Section 5.3.3.3 Additional Variables
Previously read:

Additional pre-specified endpoints include but are not limited to the following:

- Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.
- Assessment of the relationship between adalimumab serum concentrations and efficacy during induction and maintenance by Week 8 response status.
- Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.
- Proportion of subjects who are taking corticosteroids at Baseline and are steroid free over time.
- Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.
- Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score ≤ 2 with no subscore > 1) score over time.
- Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of ≥ 2 points and ≥30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) over time.

- Change from Baseline in hs-CRP over time.
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in IBDQ score over time.
- Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.
- Change from Baseline in SF-36 score over time.
- Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic improvement at Week 52.
- All-cause and UC-related hospitalization and surgery rates during Weeks 0 – 8.
- All cause and UC-related hospitalization and surgery rates during Weeks 8 – 52.
- Change from Baseline in fecal calprotectin over time.
- Time to achievement of remission (per Partial Mayo score)
- Time to achievement of response (per Partial Mayo score)
- Time to loss of response and factors associated with loss of response.
- Change from Baseline in histologic score at Week 8.
- Change from Baseline in histologic score at Week 52.
- Proportion of subjects achieving clinical remission per Full Mayo score, excluding the PGA subscore (defined as Full Mayo Score, excluding the PGA subscore, ≤ 2 with no subscore > 1) at Week 8.

- Proportion of Week 8 responders (per Full Mayo score) achieving clinical remission (per Full Mayo score, excluding the PGA subscore) at Week 52.
- Change in presence of extraintestinal manifestations over time.

Has been changed to read:

Additional pre-specified endpoints in the Induction Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Induction Study.
- All-cause and UC-related hospitalization and surgery rates during Weeks 0 – 8.
- Change from Baseline in histologic score at Week 8.
- Proportion of subjects achieving clinical remission per Adapted Mayo Score (defined as stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1) at Week 8.
- Proportion of subjects achieving Full Mayo score excluding the PGA subscore, ≤ 2 with no subscore > 1 at Week 8.
- Relationship between histologic subscores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 8.
- Relationship between histologic scores and endoscopic subscore of 0 as Week 8.

Additional pre-specified endpoints in the Maintenance Study include but are not limited to the following:

- Assessment of the relationship between adalimumab serum concentrations and efficacy during the Maintenance Study by Week 8 response status.
- Proportion of Week 8 responders (per Full Mayo score) with clinical response at Week 52.
- Proportion of Week 8 non-responders (per Full Mayo score) with clinical response at Week 52.

- Proportion of Week 8 non-responders (per Full Mayo score) with endoscopic improvement at Week 52.
- All cause and UC-related hospitalization and surgery rates during Weeks 8 – 52.
- Change from Baseline in histologic score at Week 52.
- Proportion of Week 8 responders per Adapted Mayo score (defined as decrease from Baseline in the Adapted Mayo Score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1) achieving clinical remission per Adapted Mayo scores at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) achieving Full Mayo Score, excluding the PGA subscore ≤ 2 with no subscore > 1 at Week 52.
- Relationship between histologic scores and endoscopic improvement (endoscopy subscore of 0 or 1) at Week 52.
- Relationship between histologic scores and endoscopic subscore of 0 at Week 52.
- Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 180 days and in clinical remission (per Full Mayo score) at Week 52.

The following additional pre-specified endpoints will also be analyzed in both the Induction Study and the Maintenance Study.

- Analysis of the impact of immunogenicity on safety, pharmacokinetics, and efficacy.
- Proportion of subjects who are taking corticosteroids at Baseline and are steroid free over time.
- Evaluation of adalimumab concentrations and immunogenicity at the time of loss of clinical remission.
- Proportion of subjects achieving clinical remission per Partial Mayo (defined as a Partial Mayo score ≤ 2 with no subscore > 1) score over time.
- Proportion of subjects achieving clinical response per Partial Mayo score (defined as a decrease in Partial Mayo score of ≥ 2 points and ≥ 30% from

Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) over time.

- Change from Baseline in hs-CRP over time.
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in IBDQ score over time.
- Change from Baseline in Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in work productivity and impairment questionnaire (WPAI) scores over time.
- Change from Baseline in SF-36 score over time.
- Change from Baseline in fecal calprotectin over time.
- Time to achievement of remission (per Partial Mayo score)
- Time to achievement of response (per Partial Mayo score)
- Time to loss of response and factors associated with loss of response.
- Change in presence of extraintestinal manifestations over time.

Section 5.3.4 Pharmacokenetic Variables
First sentence previously read:

Serum concentrations of adalimumab at each scheduled sampling time will be summarized and stratified by treatment arm.

Has been changed to read:

Serum concentrations of adalimumab at each scheduled sampling time will be summarized and stratified by treatment regimen.

Section 5.5.1 Treatments Administered
Previously read:

Double-Blind Induction Period

At Baseline (Week 0), subjects will be randomized 3:2 to one of two double-blind adalimumab induction doses.

Subjects assigned to the standard induction arm will receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and matching placebo (4 syringes) at Week 1. At Week 2, subjects will receive 80 mg (2 syringes) and matching placebo (2 syringes) At Week 3, subjects will receive matching placebo (4 syringes) and at Weeks 4 and 6, subjects will receive a dosing regimen of 40 mg (1 syringe).

Subjects assigned to the higher induction arm will receive 160 mg (4 syringes) at Weeks 0, 1, 2, and 3 followed by 40 mg (1 syringe) at Weeks 4 and 6.

Double-Blind Maintenance Doses

At Week 8, subjects will be re-randomized to receive 1 of 3 double-blind adalimumab treatment maintenance regimens in a 2:2:1 ratio.

Subjects assigned to the adalimumab 40 mg eow arm will receive 40 mg (1 syringe) at Weeks 8, 10, 12, 14, 16, 18, 20, 22, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and 50. Subjects will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24. At Week 37, subjects will receive matching placebo (4 syringes). Matching Placebo (1 syringe) will be administered at Weeks 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52.

Subjects assigned to the adalimumab 40 mg ew arm will receive 40 mg (1 syringe) at Weeks 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. Subjects will receive 40 mg (1 syringe) and placebo (3 syringes) at Weeks 24 and 37. No dose will be administered at Week 52.

Subjects assigned to the TDM arm will receive adalimumab 40 mg eow (1 syringe) at Week 8 and Week 10. Matching placebo (1 syringe) will be administered at Weeks 9 and 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria in Table 1.

Subjects who don't dose escalate at Week 12 will receive 40 mg eow (1 syringe) at Weeks 12, 14, 16, 18, 20, and 22 and placebo (1 syringe) at Weeks 13, 15, 17, 19, 21 and 23. Subjects who escalate at Week 12 will receive 40 mg ew (1 syringe) at Weeks 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 and 23.

Subjects who don't dose escalate at Week 24 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg eow (1 syringe) at Weeks 26, 28, 30, 32, 34, and 36 and placebo (1 syringe) at Weeks 25, 27, 29, 31, 33 and 35. Subjects who escalate at Week 24 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36.

Subjects who don't dose escalate at Week 24 and were receiving adalimumab 40 mg ew will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36. Subjects who escalate at Week 24 and were receiving adalimumab 40 mg ew will receive 160 mg (4 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36.

Subjects who don't dose escalate at Week 37 and were receiving adalimumab 40 mg eow will receive placebo (4 syringes) at Week 37, followed by 40 mg eow (1 syringe) at Weeks 38, 40, 42, 44, 46, 48, and 50 and placebo (1 syringe) at Weeks 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52.

Subjects who escalate at Week 37 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 37, followed by 40 mg ew

(1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52.

Subjects who don't dose escalate at Week 37 and were receiving adalimumab 40 mg ew will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52.

Subjects who escalate at Week 37 and were receiving adalimumab 40 mg ew will receive 160 mg (4 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52.

Has been changed to read:

Double-Blind Induction Study

At Baseline (Week 0), subjects will be randomized 3:2 to one of two double-blind adalimumab induction dosing regimens.

Subjects assigned to the standard induction dosing regimen will receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and matching placebo (4 syringes) at Week 1. At Week 2, subjects will receive 80 mg (2 syringes) and matching placebo (2 syringes) At Week 3, subjects will receive matching placebo (4 syringes) and at Weeks 4 and 6, subjects will receive a dosing regimen of 40 mg (1 syringe).

Subjects assigned to the higher induction dosing regimen will receive 160 mg (4 syringes) at Weeks 0, 1, 2, and 3 followed by 40 mg (1 syringe) at Weeks 4 and 6.

Double-Blind Maintenance Study

At Week 8, subjects will be re-randomized to receive 1 of 3 double-blind adalimumab treatment maintenance regimens in a 2:2:1 ratio.

Subjects assigned to the adalimumab 40 mg eow regimen will receive 40 mg (1 syringe) at Weeks 8, 10, 12, 14, 16, 18, 20, 22, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and 50.

Subjects will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24. At Week 37, subjects will receive matching placebo (4 syringes). Matching Placebo (1 syringe) will be administered at Weeks 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects assigned to the adalimumab 40 mg ew regimen will receive 40 mg (1 syringe) at Weeks 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. Subjects will receive 40 mg (1 syringe) and placebo (3 syringes) at Weeks 24 and 37. No dose will be administered at Week 52/Premature Discontinuation.

Subjects assigned to the TDM regimen will receive adalimumab 40 mg eow (1 syringe) at Week 8 and Week 10. Matching placebo (1 syringe) will be administered at Weeks 9 and 11. At Weeks 12, 24 and 37, the regimen will be adjusted for subjects meeting specified criteria in Table 1.

Subjects who don't dose escalate at Week 12 will receive 40 mg eow (1 syringe) at Weeks 12, 14, 16, 18, 20, and 22 and placebo (1 syringe) at Weeks 13, 15, 17, 19, 21 and 23. Subjects who escalate at Week 12 will receive 40 mg ew (1 syringe) at Weeks 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 and 23.

Subjects who don't dose escalate at Week 24 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg eow (1 syringe) at Weeks 26, 28, 30, 32, 34, and 36 and placebo (1 syringe) at Weeks 25, 27, 29, 31, 33 and 35. Subjects who escalate at Week 24 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36.

Subjects who don't dose escalate at Week 24 and were receiving adalimumab 40 mg ew will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36. Subjects who escalate at Week 24 and were receiving adalimumab 40 mg ew will receive 160 mg

(4 syringes) at Week 24, followed by 40 mg ew (1 syringe) at Weeks 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36.

Subjects who don't dose escalate at Week 37 and were receiving adalimumab 40 mg eow will receive placebo (4 syringes) at Week 37, followed by 40 mg eow (1 syringe) at Weeks 38, 40, 42, 44, 46, 48, and 50 and placebo (1 syringe) at Weeks 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects who escalate at Week 37 and were receiving adalimumab 40 mg eow will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects who don't dose escalate at Week 37 and were receiving adalimumab 40 mg ew will receive 40 mg (1 syringe) and placebo (3 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects who escalate at Week 37 and were receiving adalimumab 40 mg ew will receive 160 mg (4 syringes) at Week 37, followed by 40 mg ew (1 syringe) at Weeks 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

Section 5.5.3 Method of Assigning Subjects to Treatment Arms
Section title previously read:

Method of Assigning Subjects to Treatment Arms

Has been changed to read:

Method of Assigning Subjects to Treatment Regimens

Section 5.5.3 Method of Assigning Subjects to Treatment Arms
First and second paragraph previously read:

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 Week 0 in a 3:2 ratio into the criteria-driven arms using the IRT, which will assign a randomization number according to the randomization scheme, generated by AbbVie before the start of the study. The randomization will be stratified by previous infliximab use and Baseline corticosteroid use. The criteria-driven arm assignment will be maintained by the IRT. Subjects will be referred to by the subject number assigned at Screening.

Subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Period at the conclusion of the Week 8 Visit to one of three treatment arms in a 2:2:1 ratio. Subjects will be re-stratified by: induction treatment regimen and response status (per Full Mayo Score) at Week 8. Among Week 8 responders, the randomization will be further stratified by remission status (per Full Mayo Score) at Week 8.

Has been changed to read:

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 Induction Study. Subjects who enter the Induction Study will be randomized at Week 0 in a 3:2 ratio into the criteria-driven regimens using the IRT, which will assign a randomization number according to the randomization scheme, generated by AbbVie before the start of the study. The randomization will be stratified by previous infliximab use and Baseline corticosteroid use. The criteria-driven regimen assignment will be maintained by the IRT. Subjects will be referred to by the subject number assigned at Screening.

Subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Study at the conclusion of the Week 8 Visit to one of three treatment regimens in a 2:2:1 ratio. Subjects will be re-stratified by: induction treatment regimen and response status (per Full Mayo Score) at Week 8. Among Week 8 responders, the randomization will be further stratified by remission status (per Full Mayo Score) at Week 8.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Second paragraph, last sentence previously read:

The subject must record all dosing information in the subject diary.

Has been changed to read:

The subject must record all home dosing information in the subject diary.

Section 5.5.6 Treatment Compliance
Second paragraph, third sentence previously read:

In order to document compliance with the treatment regimen, the subject will be given a diary to record all injection dates and times.

Has been changed to read:

In order to document compliance with the treatment regimen, the subject will be given a diary to record all injection dates and times administered at home.

Section 5.6.1 Discussion of Study Design and Choice of Control Arms
Section title previously read:

Discussion of Study Design and Choice of Control Arms

Has been changed to read:

Discussion of Study Design and Choice of Control Regimens

Section 5.6.1 Discussion of Study Design and Choice of Control Arms
First paragraph, second sentence previously read:

No placebo arm is planned due to documented efficacy of adalimumab in UC and the purpose of this study is to investigate whether greater efficacy is achieved with the higher dose than with the standard dose, and to compare safety outcomes.

Has been changed to read:

No placebo regimen is planned due to documented efficacy of adalimumab in UC and the purpose of this study is to investigate whether greater efficacy is achieved with the higher dose than with the standard dose, and to compare safety outcomes.

Section 5.6.1 Discussion of Study Design and Choice of Control Arms
Last paragraph previously read:

The primary study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active UC.

Has been changed to read:

The study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active UC.

Section 5.6.4 Selection of Doses in the Study
Subsection <u>Maintenance Dose Selection</u>
First paragraph, third and fourth sentence previously read:

An exploratory arm evaluating a TDM strategy will also be evaluated. The goal of the TDM maintenance dosing arm is to analyze the feasibility, efficacy, and safety of aiming for serum adalimumab levels within a targeted concentration range for making decisions regarding dosing.

Has been changed to read:

An exploratory regimen evaluating a TDM strategy will also be evaluated. The goal of the TDM maintenance dosing regimen is to analyze the feasibility, efficacy, and safety of

aiming for serum adalimumab levels within a targeted concentration range for making decisions regarding dosing.

Section 5.6.4 Selection of Doses in the Study
Subsection Maintenance Dose Selection
Second paragraph, first sentence previously read:

The targeted concentration range selected for the TDM arm was based on serum concentrations observed during Study M06-827 and the mean serum concentrations observed in subjects who achieved remission during this study.

Has been changed to read:

The targeted concentration range selected for the TDM dosing regimen was based on serum concentrations observed during Study M06-827 and the mean serum concentrations observed in subjects who achieved remission during this study.

Section 5.6.4 Selection of Doses in the Study
Subsection Maintenance Dose Selection
Last paragraph, last sentence previously read:

Based on observed adalimumab pharmacokinetics in Study M06-827, it is expected that approximately 60% of subjects in the TDM arm will escalate to 40 mg weekly dosing, and approximately 15% will receive re-induction thereafter using this concentration range and the RBS criteria described in Table 1 as a guide to adjust dosing.

Has been changed to read:

Based on observed adalimumab pharmacokinetics in Study M06-827, it is expected that approximately 60% of subjects in the TDM dosing regimen will escalate to 40 mg weekly dosing, and approximately 15% will receive re-induction thereafter using this concentration range and the RBS criteria described in Table 1 as a guide to adjust dosing.

Section 6.1.4 Adverse Event Collection Period
Third paragraph, second sentence previously read:

Thus, all SAEs and non-serious AEs, as defined by AbbVie, reported during the 70-day follow-up phone call must be captured in the clinical database (Appendix J.

Has been changed to read:

Thus, all SAEs and non-serious AEs, as defined by AbbVie, as well as the medication for AEs/SAEs, reported during the 70-day follow-up phone call must be captured in the clinical database via the eCRF and also recorded in source documentation (Appendix J).

Section 6.1.5 Adverse Event Reporting
Second paragraph, "Dept." previously read:

[redacted]

Has been changed to read:

[redacted]

Section 6.1.5 Adverse Event Reporting
Fourth paragraph, "address" previously read:

Primary Study Designated Physician

[redacted] MD
[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

Has been changed to read:

Primary Study Designated Physician

[redacted] MD
[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

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

Alternate Contact:

[redacted] MD
[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

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

Has been changed to read:

Alternate Contact:

[redacted] MD
[redacted]
Immunology Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

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

Section 8.1 Statistical and Analytical Plans
First paragraph previously read:

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis. The statistical analyses described in this section are for the main study (i.e., will be restricted to subjects recruited in the non-Japan sites).

Has been changed to read:

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis. The following statistical analysis plan is for subjects recruited in the main study. A separate statistical analysis plan will be provided for subjects recruited in the Japan sub-study and for all the subjects recruited in the main study and the Japan sub-study (See Appendix K).

Section 8.1.1 Analysis Population
Second and third paragraph previously read:

Intent-to-Treat (ITT) population includes all subjects who were randomized. ITT subjects will be analyzed as randomized. ITT is the primary population for the efficacy analysis at Week 8 during the induction period.

Intent-to-Treat maintenance (ITT-M) population includes all subjects who are re-randomized at Week 8. ITT-M subjects will be analyzed as randomized. ITT-M is the primary population for the efficacy analysis at Week 52 during the maintenance period.

Has been changed to read:

Intent-to-Treat (ITT1) population includes all subjects who were randomized at Baseline. ITT1 subjects will be analyzed as randomized. ITT1 is the primary population for the efficacy analysis at Week 8 during the Induction Study.

Intent-to-Treat maintenance (ITT2) population includes all subjects who are re-randomized at Week 8 to the Maintenance Study. ITT2 subjects will be analyzed as randomized. ITT2 is the primary population for the efficacy analysis at Week 52 during the Maintenance Study.

Section 8.1.1 Analysis Population
Last paragraph, first sentence previously read:

The Safety set consists of all randomized subjects who received at least one injection of study drug.

Has been changed to read:

The Safety set consists of all subjects who received at least one injection of study drug.

Section 8.1.3 Demographics and Baseline Characteristics
Second sentence previously read:

The p-value will be provided to assess the comparability of the treatment arms assigned by randomization.

Has been changed to read:

The p-value will be provided to assess the comparability of the treatment groups assigned by randomization.

Section 8.1.4.1 Primary Efficacy Variable
Section title and text previously read:

8.1.4.1 Primary Efficacy Variable

The primary efficacy endpoint is:

Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary analysis will compare the subjects in the higher adalimumab induction arm versus the standard adalimumab induction arm in the ITT analysis set. The difference between the treatment arms in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between treatment arms will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 8 endpoint. Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non-responders.

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as IMM use at

Baseline, Baseline CRP, and disease severity at Baseline will also be performed for the primary endpoint.

For CMH test statistic, if the condition of each stratum to have at least one subject with each treatment and at least one subject with each possible outcome is violated for the primary approach to the primary efficacy endpoint, the stratification factor Baseline corticosteroid use will be dropped from the CMH model in the analysis of all categorical variables.

Has been changed to read:

8.1.4.1 Primary Efficacy Variables

The primary efficacy endpoint for the Induction Study is:

Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

The primary analysis of the Induction Study will compare the subjects in the higher adalimumab induction regimen versus the standard adalimumab induction regimen in the ITT1 analysis set. The difference between the treatment regimens in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use at Baseline. A CMH based two sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the

Week 8 endpoint. Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non responders.

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint for the Induction Study.

The primary analysis of the Maintenance Study will compare the Week 8 responders (per Full Mayo Score) in the eow regimen versus the subjects in the ew regimen in the ITT2 analysis set. The difference between the treatment regimens in the proportion of subjects achieving clinical remission at Week 52 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for Induction treatment regimen and the remitter status (per Full Mayo Score) at Week 8. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 52 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 52 endpoint. Subjects with missing Mayo score data for Week 52 will also be classified as Week 52 non-responders.

The TDM regimen will be used for exploratory analyses.

Section 8.1.4.2 Secondary Efficacy Variables
Previously read:

The 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 an alpha level of 0.050 (two-sided) in ranked endpoint order until the significant level exceeds 0.05. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables. For Week 8 endpoints, the difference between the higher adalimumab induction arm versus the standard adalimumab induction arm will be assessed using ITT analysis set. For Week 52 endpoints, the

difference between the eow arm versus the ew arm will be assessed using Intent-to-Treat maintenance (ITT-M) analysis set where Week 8 responder/remitter status will be determined based on the Full Mayo score using endoscopy subscore from the central reader. Categorical data will be described by frequency and percentage; continuous data will be described by mean, standard deviation, minimum, median, and maximum. In general, the secondary endpoints at Week 8 that are of the binary type will be analyzed using a two-sided CMH test adjusted for previous infliximab use and Baseline corticosteroid use in the ITT analysis set, and the secondary endpoints at Week 52 that are of the binary type will be analyzed using a two-sided CMH test adjusted for induction treatment regimen, and remitter status (per Full Mayo score) at Week 8 (where applicable) in the ITT-M analysis set. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. Continuous secondary efficacy variables will be analyzed using Analysis of Covariance (ANCOVA) with factor for treatment arm, stratification variables and Baseline values. NRI for missing data will be used for categorical endpoints. Procedures for handling missing data for continuous endpoints will be described in the Statistical Analysis Plan.

Has been changed to read:

The 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 an alpha level of 0.050 (two-sided) in ranked endpoint order until the significant level exceeds 0.05. No additional statistically significant treatment differences could be declared if the preceding ranked endpoint fails to achieve 0.05. The second group includes all other additional secondary variables. For the Induction Study endpoints, the difference between the higher adalimumab induction regimen versus the standard adalimumab induction regimen will be assessed using ITT1 analysis set. For the Maintenance Study endpoints, the difference between the eow dosing regimen versus the ew doing regimen will be assessed using Intent-to-Treat maintenance (ITT2) analysis set where Week 8 responder/remitter status will be determined based on the Full Mayo score using endoscopy subscore from the central reader. Categorical data will be described by

frequency and percentage; continuous data will be described by mean, standard deviation, minimum, median, and maximum. In general, the secondary endpoints at Week 8 that are of the binary type will be analyzed using a two-sided CMH test adjusted for previous infliximab use and Baseline corticosteroid use in the ITT1 analysis set, and the secondary endpoints at Week 52 that are of the binary type will be analyzed using a two-sided CMH test adjusted for induction treatment regimen, and remitter status (per Full Mayo score) at Week 8 (where applicable) in the ITT2 analysis set. Additionally, the two-sided 95% confidence interval for the difference in proportions will be provided. Continuous secondary efficacy variables will be analyzed using Analysis of Covariance (ANCOVA) with factor for treatment regimen, stratification variables and Baseline values. NRI for missing data will be used for categorical endpoints. Procedures for handling missing data for continuous endpoints will be described in the Statistical Analysis Plan.

Section 8.1.5 Statistical Analyses of Safety
Previously read:

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 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 medication and within 70 days after the last dose of the study medication. Treatment-emergent AEs will be summarized separately for the double-blind induction period (Week 0 to Week 8), double-blind maintenance period (Week 8 to 70 days after the last dose of the study medication), and Study M14-033 (Week 0 to 70 days after the last dose of the study medication). An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to PD (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. Other safety variables like laboratory data will be described by descriptive statistics. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

Has been changed to read:

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 Studies using the safety analysis set which includes all subjects who receive at least one dose of study medication in each Study respectively. Treatment-emergent AEs, will be tabulated by MedDRA preferred term by treatment group for the Induction Study and the Maintenance Study, and for any adalimumab over the entire study. Mean changes in vital signs, physical examination results, ECGs, and clinical laboratory data values will be analyzed.

Section 8.1.6 Other Statistical Analyses of Efficacy
First paragraph previously read:

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

Has been changed to read:

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

Section 8.1.7 Interim Analysis
Previously read:

An interim analysis of the primary endpoint and ranked secondary efficacy variables for Week 8 only as well as safety data collected from Baseline through double-blind Week 8 will be performed after the last subject in ITT population completes the 8-week double-blind period of the main study. A database lock 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 primary efficacy endpoint of the main study, no adjustment of alpha-level is necessary.

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 8 may be performed after the last subject in ITT1 population completes the 8-week double-blind Induction Study of the main 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 primary efficacy endpoint of the Induction Study, no adjustment of alpha-level is necessary.

Section 8.1.8 Pharmacokinetic Analysis
First paragraph, first sentence previously read:

Adalimumab trough serum concentrations will be summarized by treatment arm at each time point using descriptive statistics.

Has been changed to read:

Adalimumab trough serum concentrations will be summarized by treatment regimen at each time point using descriptive statistics.

Section 8.2 Determination of Sample Size
Previously read:

Subjects will be randomized to the adalimumab higher induction arm and the adalimumab standard induction arm in a 3:2 ratio. The sample size calculations for the main study are based on a two-sided Fisher's exact test at a significance level of 0.05. Assuming an expected Week 8 endoscopic improvement rate of 60% in the adalimumab higher induction dose arm and 45% in the adalimumab standard induction dose arm, 525 subjects (315 in the higher induction dose arm and 210 in the standard induction dose arm) will provide 90% statistical power to detect the difference between the two induction treatment arms. This sample size of 525 subjects in the main study will provide at least 95% power to detect a treatment difference of 15% for the primary endpoint of clinical remission, assuming an expected Week 8 clinical remission rate of 35% in the adalimumab higher induction arm and 20% in the adalimumab standard induction arm.

Assuming the average response rate at Week 8 in the adalimumab induction dose arms in the main study is 60%, there will be 315 responders for the analysis of Week 52 clinical

remission among the Week 8 responders (126 in the higher maintenance dose arm, 126 in the standard maintenance dose arm, and 63 in the TDM regimen arm). This sample size will provide 80% power to detect a treatment difference of 18%, assuming an expected Week 52 clinical remission rate of 48% in the adalimumab higher maintenance arm and 30% in the adalimumab standard maintenance arm.

The sample size calculations for the Japan sub-study are described in Appendix K.

Has been changed to read:

When Protocol M14-033 was initially designed, AbbVie used an assumption regarding induction response rate in order to calculate the expected number of Week 8 responders that would comprise the analysis set used to compare the Week 52 remission rates in the adalimumab 40 mg every other week and 40 mg weekly groups. AbbVie assumed that the overall response rate (per Full Mayo Score) at Week 8 would be 60%, which would provide 315 Week 8 responders for the analysis of Week 52 remission (126 in the every other week dosing group, 126 in the every week dosing group, and 63 in the exploratory TDM group, based upon a 2:2:1 randomization scheme) from the 525 randomized induction subjects. This sample size would provide 80% power to detect a treatment difference of 18%, assuming an expected Week 52 remission rate of 48% in the adalimumab weekly dosing group and 30% in the adalimumab every other week dosing group.

Considering the uncertainty in the Week 8 response rate may be caused by the impact of central reading on the endoscopic subscore, based on the ozanimod Phase 2 TOUCHSTONE trial data presented in early 2015, AbbVie re-estimated the Week 8 response rate to be 50% instead of 60%. Under this assumption, if the sample remains 525, a smaller size of the Week 52 analysis set than was original predicted, and thus an insufficient power (72%) for the analysis of the Week 52 remission endpoint is expected. Furthermore, Week 52 remission rate will be the primary endpoint of the Maintenance Study. AbbVie proposes to increase the power for this endpoint from 80% as originally designed to 90% retaining the currently assumed treatment difference. The combined

impact of these changes (i.e., increased power plus higher uncertainty in Week 8 response rate) results in an increase in the overall Study M14-033 sample size from 525 subjects to a total of 840 subjects.

Subjects will be randomized to the adalimumab higher induction regimen and the adalimumab standard induction regimen in a 3:2 ratio. The sample size calculations for the main study are based on a two sided Fisher's exact test at a significance level of 0.05. Assuming an expected Week 8 endoscopic improvement rate of 60% in the adalimumab higher induction dosing regimen and 45% in the adalimumab standard induction dosing regimen, 804 subjects (504 subjects in the higher induction dosing regimen and 336 subjects in the standard induction dosing regimen) will provide 90% statistical power to detect the difference between the two induction treatment regimens. This sample size of 804 subjects in the main study will provide at least 95% power to detect a treatment difference of 15% for the primary endpoint of clinical remission, assuming an expected Week 8 clinical remission rate of 35% in the adalimumab higher induction regimen and 20% in the adalimumab standard induction regimen.

Assuming the average response rate at Week 8 in the adalimumab induction dosing regimens in the main study is 50%, there will be 420 responders for the analysis of Week 52 clinical remission among the Week 8 responders (168 in the higher maintenance dosing regimen, 168 in the standard maintenance dosing regimen, and 84 in the TDM regimen). This sample size will provide 90% power to detect a treatment difference of 18%, assuming an expected Week 52 clinical remission rate of 48% in the adalimumab higher maintenance dosing regimen and 30% in the adalimumab standard maintenance dosing regimen.

The sample size calculations for the Japan sub-study are described in Appendix K.

Section 8.3 Randomization Methods
Second paragraph, first sentence previously read:

At the conclusion of the 8-week Induction Period, all subjects will be re-randomized into the 44-week Maintenance Period.

Has been changed to read:

At the conclusion of the 8-week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study.

Section 8.3 Randomization Methods
Second paragraph, last sentence previously read:

All subjects will be randomized into one of three blinded treatment arms in a 2:2:1 ratio:

Has been changed to read:

All subjects will be randomized into one of three blinded treatment regimens in a 2:2:1 ratio:

Section 8.3 Randomization Methods
Last bullet previously read:

Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory arm). (The Japan sub-study does not have a TDM arm. Subjects will be randomized into Adalimumab 40 mg eow arm or Adalimumab 40 mg ew arm in a 1:1 ratio.)

Has been changed to read:

Adalimumab Therapeutic Drug Monitoring (TDM) regimen (exploratory). (The Japan sub-study does not have a TDM regimen. Subjects will be randomized into Adalimumab 40 mg eow or Adalimumab 40 mg ew treatment regimens in a 1:1 ratio.)

Section 11.0 Data Quality Assurance
Previously read:

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

Has been changed to read:

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.

Data from the central laboratory and the imaging vendor will be electronically transferred to the study database.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	
[redacted]	[redacted]	Data and Statistical Sciences
[redacted]	[redacted]	Clinical Pharmacokinetics and Pharmacodynamics
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Data and Statistical Sciences
[redacted]	[redacted]	Clinical Pharmacokinetics and Pharmacodynamics
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Clinical
[redacted]	[redacted]	Bioanalysis

Appendix J. 70-Day Follow-Up Phone Call – Sample
Previously read:

Site Name/Number: _____

Subject Number: _____

Please contact subjects who discontinue adalimumab 70 days following study drug discontinuation.

Date of Call: _____

- ☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt.)
- ☐ No Events Reported
- ☐ N/A subject continued adalimumab therapy after the end of their study participation

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.)

_____

_____

_____

_____

_____

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

Please fax all completed forms to:

[Name] at XXX-XXX-XXXX

Has been changed to read:

Site Name/Site Number: _____

Subject Number: _____

Date of last study drug administration (DD/MMM/YY): _____

Please contact subjects who discontinue adalimumab 70 days following study drug discontinuation.

Note: Subjects who continue commercial adalimumab do not require a 70-day follow-up call.

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
- ☐ AEs/SAEs Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.) Any medications taken as a result of the events should also be entered on the eCRF.

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

If 70-day follow-up call was not performed:

- ☐ Subject continued adalimumab therapy after the end of their study participation
- ☐ Other, describe below:

Please fax all completed forms to:

Fax: [redacted]

Email: [redacted]

Subject line: PI NAME_Subject number_70 day followup

Appendix K. Japan Sub-Study
Section 4.0 Study Objective
Previously read:

The primary study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis.

Has been changed to read:

The study objective is to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis.

Appendix K. Japan Sub-Study
Section 5.1 Overall Study Design and Plan: Description
Previously read:

The primary analysis for the Japan sub-study will be an analysis of subjects achieving clinical remission (per Full Mayo Score) at Week 8. The analysis will include approximately 80 subjects (48 in the higher induction dose regimen and 32 in the standard induction dose regimen) from 21 Japanese sites and approximately 525 subjects from all other sites in the main study.

Has been changed to read:

The primary analysis for the Japan sub-study during the Induction Study will be an analysis of subjects achieving clinical remission (per Full Mayo Score) at Week 8. The primary analysis for the Japan sub-study during the Maintenance Study will be an analysis of subjects is the proportion of Week 8 responders achieving clinical remission (per Full Mayo score) at Week 52.

The analysis will include approximately 100 subjects (60 in the higher induction dose regimen and 40 in the standard induction dose regimen) from 21 Japanese sites and approximately 840 subjects from all other sites in the main study.

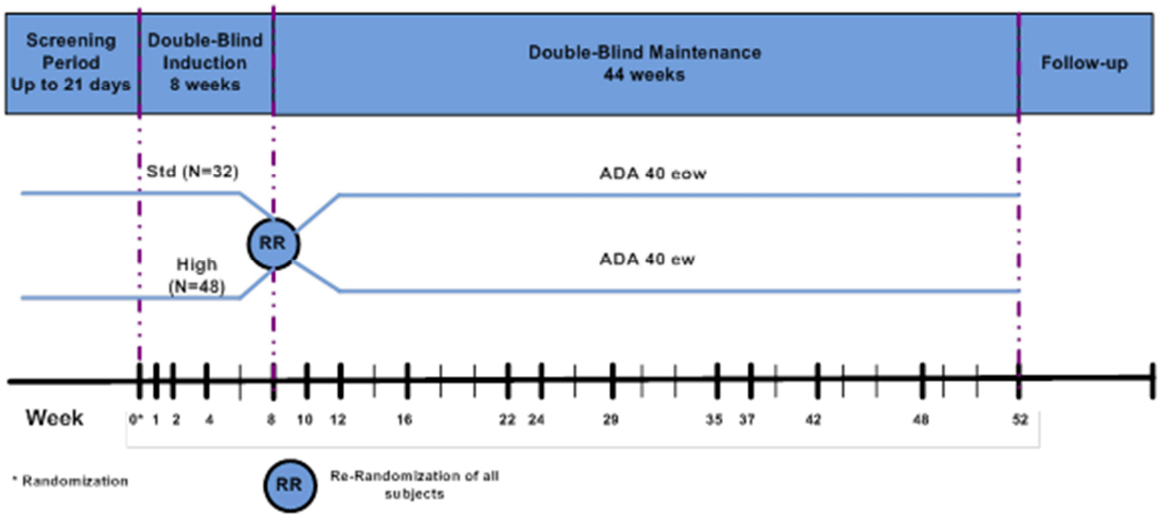
Appendix K. Japan Sub-Study
Section 5.1 Overall Study Design and Plan: Description
Subsection <u>44-Week Double-Blind Maintenance Period</u>
Subsection title and text previously read:

<u>44-Week Double-Blind Maintenance Period</u>

The TDM arm in the maintenance period will not be applied to the Japan sub-study because of logistical challenges in obtaining adalimumab serum concentration results within the time period specified in the main study. At the conclusion of the 8-Week Double-Blind Induction Period, subjects will return to the study site and will be re-randomized using the same stratification variables as the main study via IRT into the

44-Week Double-Blind Maintenance Period to one of two treatment arms in a 1:1 ratio with the same stratification from the main study:

- Adalimumab 40 mg eow
- Adalimumab 40 mg every week (ew)



Subjects in the adalimumab 40 mg eow arm will continue to receive 40 mg eow until the end of the study. Subjects in the adalimumab 40 mg ew arm will start 40 mg ew at Week 8 until the end of the study.

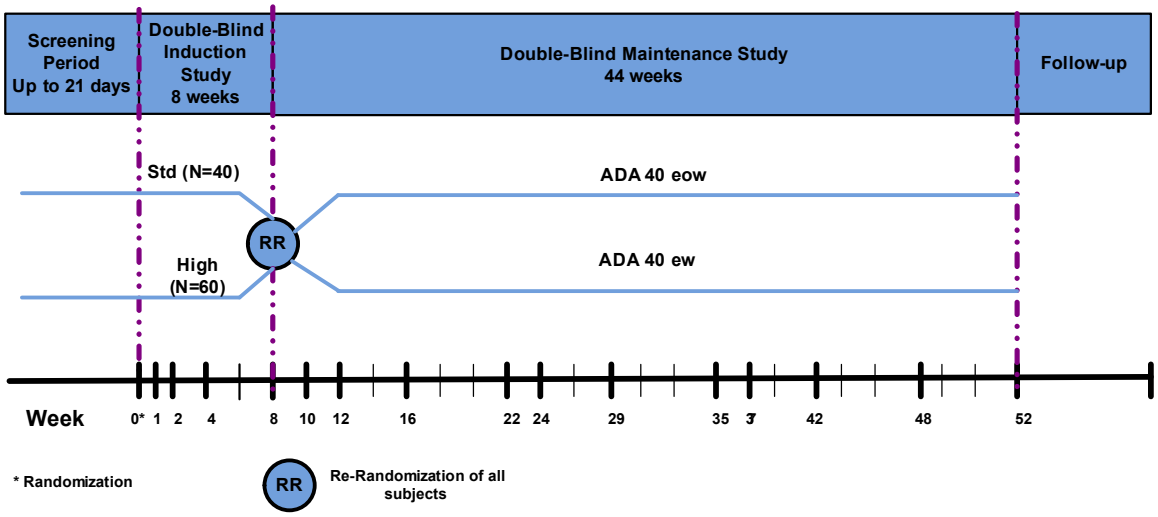
Has been changed to read:

<u>44-Week Double-Blind Maintenance Study</u>

The TDM regimen in the maintenance period will not be applied to the Japan sub-study because of logistical challenges in obtaining adalimumab serum concentration results within the time period specified in the main study. At the conclusion of the 8-Week Double-Blind Induction Study, subjects will return to the study site and will be re-randomized using the same stratification variables as the main study via IRT into the

44-Week Double-Blind Maintenance Study to one of two treatment groups in a 1:1 ratio with the same stratification from the main study:

- Adalimumab 40 mg eow
- Adalimumab 40 mg every week (ew)



Subjects in the adalimumab 40 mg eow treatment group will continue to receive 40 mg eow until the end of the study. Subjects in the adalimumab 40 mg ew treatment group will start 40 mg ew at Week 8 until the end of the study.

Appendix K. Japan Sub-Study
Section 5.2.2 Exclusion Criteria
Criterion 25 previously read:

25. Subjects with a positive result for 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 (+)

Has been changed to read:

25. Subjects with a positive result for 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.

Appendix K. Japan Sub-Study
Table 2. Study Activities
Header row, column "8-Week Double-Blind Induction Period" and "44-Week Double-Blind Maintenance Period" previously read:

"8-Week Double-Blind Induction Period" and "44-Week Double-Blind Maintenance Period"

Has been changed to read:

"8-Week Double-Blind Induction Study" and "44-Week Double-Blind Maintenance Study"

Appendix K. Japan Sub-Study
Table 2. Study Activities
Table note "j."
Add: new last sentence

Further explanations of these tests are provided in the Laboratory Manual.

Appendix K. Japan Sub-Study
Table 2. Study Activities
Table note "m."
Add: new last sentence

Remaining sample will be stored for potential research testing.

Appendix K. Japan Sub-Study
Section 5.3.2 Drug Concentration Measurements
Subsection <u>Collection of Samples for Adalimumab and AAA Assays</u>
Last paragraph, last sentence previously read:

The total number of samples planned (not including unscheduled visit sample collections) will not exceed 1,200 (15 samples × 80 subjects) for the adalimumab assay and 560 (7 samples × 80 subjects) for the AAA assay for the sub-study.

Has been changed to read:

The total number of samples planned (not including unscheduled visit sample collections) will not exceed 1,500 (15 samples × 100 subjects) for the adalimumab assay and 700 (7 samples × 100 subjects) for the AAA assay for the sub-study.

Appendix K. Japan Sub-Study
Section 5.3.2 Drug Concentration Measurements
Subsection Collection of Samples for Infliximab and HACA Assays
Last paragraph previously read:

The total number of samples planned for Japan will not exceed 160 (2 samples × 80 subjects) for the sub-study.

Has been changed to read:

The total number of samples planned for Japan will not exceed 200 (2 samples × 100 subjects) for the sub-study.

Appendix K. Japan Sub-Study
Section 5.5.1 Treatments Administered
Previously read:

Double-Blind Induction Period

At Baseline (Week 0), subjects will be randomized 3:2 to one of two double-blind adalimumab induction doses.

Subjects assigned to the standard induction arm will receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and matching placebo (4 syringes) at Week 1. At Week 2, subjects will receive 80 mg (2 syringes) and matching placebo (2 syringes). At Week 3, subjects will receive matching placebo (4 syringes) and at Weeks 4 and 6, subjects will receive a dosing regimen of 40 mg (1 syringe).

Subjects assigned to the higher induction arm will receive 160 mg (4 syringes) at Weeks 0, 1, 2, and 3 followed by 40 mg (1 syringe) at Weeks 4 and 6.

Double-Blind Maintenance Doses

At Week 8, subjects will be re-randomized to receive 1 of 2 double-blind adalimumab treatment maintenance regimens in a 1:1 ratio.

Subjects assigned to the adalimumab 40 mg eow arm will receive 40 mg (1 syringe) at Weeks 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and 50. Matching Placebo (1 syringe) will be administered at Weeks 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52.

Subjects assigned to the adalimumab 40 mg ew arm will receive 40 mg (1 syringe) at Weeks 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52.

Has been changed to read:

Double-Blind Induction Study

At Baseline (Week 0), subjects will be randomized 3:2 to one of two double-blind adalimumab induction regimens.

Subjects assigned to the standard induction regimen will receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and matching placebo (4 syringes) at Week 1. At Week 2, subjects will receive 80 mg (2 syringes) and matching placebo (2 syringes). At Week 3, subjects will receive matching placebo (4 syringes) and at Weeks 4 and 6, subjects will receive a dosing regimen of 40 mg (1 syringe).

Subjects assigned to the higher induction regimen will receive 160 mg (4 syringes) at Weeks 0, 1, 2, and 3 followed by 40 mg (1 syringe) at Weeks 4 and 6.

Double-Blind Maintenance Study

At Week 8, subjects will be re-randomized to receive 1 of 2 double-blind adalimumab treatment maintenance regimens in a 1:1 ratio.

Subjects assigned to the adalimumab 40 mg eow regimen will receive 40 mg (1 syringe) at Weeks 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48 and

50. Matching Placebo (1 syringe) will be administered at Weeks 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51. No dose will be administered at Week 52/Premature Discontinuation.

Subjects assigned to the adalimumab 40 mg ew regimen will receive 40 mg (1 syringe) at Weeks 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 and 51. No dose will be administered at Week 52/Premature Discontinuation.

Appendix K. Japan Sub-Study
Section 5.5.3 Method of Assigning Subjects to Treatment Arms
Section title previously read:

Method of Assigning Subjects to Treatment Arms

Has been changed to read:

Method of Assigning Subjects to Treatment Regimens

Appendix K. Japan Sub-Study
Section 5.5.3 Method of Assigning Subjects to Treatment Arms
First paragraph, third sentence previously read:

Subjects who enter the study will be randomized at Week 0 in a 3:2 ratio into the criteria-driven arms using the IRT, which will assign a randomization number according to the randomization scheme, generated by AbbVie before the start of the study.

Has been changed to read:

Subjects who enter the study will be randomized at Week 0 in a 3:2 ratio into the criteria-driven regimens using the IRT, which will assign a randomization number according to the randomization scheme, generated by AbbVie before the start of the study.

Appendix K. Japan Sub-Study
Section 5.5.3 Method of Assigning Subjects to Treatment Arms
First paragraph, last sentence previously read:

The criteria-driven arm assignment will be maintained by the IRT.

Has been changed to read:

The criteria-driven regimen assignment will be maintained by the IRT.

Appendix K. Japan Sub-Study
Section 5.5.3 Method of Assigning Subjects to Treatment Arms
Second paragraph, first sentence previously read:

Subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Period at the conclusion of the Week 8 Visit to one of two treatment arms in a 1:1 ratio.

Has been changed to read:

Subjects will return to the study site and will be re-randomized via IRT into the 44-Week Double-Blind Maintenance Study at the conclusion of the Week 8 Visit to one of two treatment regimens in a 1:1 ratio.

Appendix K. Japan Sub-Study
Section 6.1.5 Adverse Event Reporting
Second paragraph, "Dept." previously read:

[redacted]

Has been changed to read:

[redacted]

Appendix K. Japan Sub-Study
Section 6.1.5 Adverse Event Reporting
Fourth paragraph, "address" previously read:

Primary Study Designated Physician

[redacted] MD
[redacted]
Pharmaceutical Development
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

Has been changed to read:

Primary Study Designated Physician

[redacted] MD
[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse 50
67061 Ludwigshafen, Germany

Appendix K. Japan Sub-Study
Section 6.1.5 Adverse Event Reporting
Fifth paragraph previously read:

Secondary Contact for Japan (Regional Medical Monitor)

[redacted] MD, PhD
[redacted] Japan Development
AbbVie GK
3-5-27 Mita, Minato
Tokyo, 108-6302
Japan

Office: [redacted]
Mobile:
Fax:
Email:

Has been changed to read:

Secondary Contact for Japan (Regional Medical Monitor)

[redacted] MD, PhD
[redacted] Japan Development
AbbVie GK
3-5-27 Mita, Minato
Tokyo, 108-6302
Japan

Office: [redacted]
Mobile:
Fax:
Email:

Appendix K. Japan Sub-Study
Section 8.1 Statistical and Analysis Plans
Second sentence previously read:

Efficacy analysis will be performed in the integrated Intent to Treat (ITT) set and the Japan ITT set.

Has been changed to read:

Efficacy analysis will be performed in the integrated Intent to Treat (ITT1) set and the Japan ITT1 set.

Appendix K. Japan Sub-Study
Section 8.1.1 Analysis Population
Previously read:

The integrated ITT (I-ITT) dataset includes all randomized subjects (at both Japanese sites and all other sites in the main study). The Japan ITT (J-ITT) dataset includes all subjects who were randomized at Japanese sites only and will be used for efficacy analyses of Japanese subjects separately from other subjects in the main study. The integrated Intent-to-Treat maintenance (I-ITT-M) population includes all subjects (at both Japanese sites and all other sites in the main study) who are re-randomized to 40 mg eow group and 40 mg ew group at Week 8 (subjects who are re-randomized to TDM group will not be included). The I-ITT-M subjects will be analyzed as randomized. The I-ITT-M is the primary population for the efficacy analysis at Week 52 during the maintenance period.

The J-ITT-M dataset includes all subjects who were re-randomized at Week 8 at Japanese sites only and will be used for maintenance efficacy analyses of Japanese subjects separately from other subjects in the main study.

The integrated Safety set consists of all randomized subjects (from both Japanese sites and those sites following the parent protocol) who received at least one dose of study medication. The Japan Safety set consists of all randomized subjects from Japanese sites who received at least one dose of study medication.

Has been changed to read:

The integrated ITT1 (I-ITT1) dataset includes all randomized subjects (at both Japanese sites and all other sites in the main study). The Japan ITT1 (J-ITT1) dataset includes all subjects who were randomized at Japanese sites only and will be used for efficacy analyses of Japanese subjects separately from other subjects in the main study. The integrated Intent to-Treat maintenance (I-ITT2) population includes all subjects (at both Japanese sites and all other sites in the main study) who are re randomized to 40 mg eow group and 40 mg ew group at Week 8 (subjects who are re-randomized to TDM group will not be included). The I-ITT2 subjects will be analyzed as randomized. The I-ITT2 is the primary population for the efficacy analysis at Week 52 during the maintenance study.

The J-ITT2 dataset includes all subjects who were re-randomized at Week 8 at Japanese sites only and will be used for maintenance efficacy analyses of Japanese subjects separately from other subjects in the main study.

The integrated Safety set consists of all subjects (from both Japanese sites and those sites following the parent protocol) who received at least one dose of study medication. The Japan Safety set consists of all randomized subjects from Japanese sites who received at least one dose of study medication.

Appendix K. Japan Sub-Study
Section 8.1.2 Planned Methods of Statistical Analysis
Delete: section title and text

8.1.2 Planned Methods of Statistical Analysis

All statistical tests will be two-sided at a significance level of 0.05. Descriptive statistics will be provided. These include the number of observations, means, standard deviation, minimum, median, and maximum for continuous variables; and counts and percentages for discrete variables. The analyses will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

Appendix K. Japan Sub-Study
Section 8.1.3 Demographics and Baseline Characteristics
First and second sentence previously read:

Demographics and Baseline characteristics of the study subjects will be summarized similarly as the main study for each treatment group using descriptive statistics in both the I-ITT dataset and the J-ITT dataset. The p-value will be provided to assess the comparability of the treatment arms assigned by randomization.

Has been changed to read:

Demographics and Baseline characteristics of the study subjects will be summarized similarly as the main study for each treatment group using descriptive statistics in both the I-ITT1 dataset and the J-ITT1 dataset. The p-value will be provided to assess the comparability of the treatment groups assigned by randomization.

Appendix K. Japan Sub-Study
Section 8.1.4.1 Primary Efficacy Variable
Section title and text previously read:

8.1.4.1 Primary Efficacy Variable

The primary efficacy endpoint is:

Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary analysis will be analyzed similarly as the main study using the integrated ITT set (I-ITT) and the Japan ITT (J-ITT) set. The difference between the treatment arms in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between treatment arms will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI]

method). Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non-responders.

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as IMM use at Baseline, Baseline CRP, and disease severity at Baseline will also be performed for the primary endpoint.

For CMH test statistic, if the condition of each stratum to have at least one subject with each treatment and at least one subject with each possible outcome is violated for the primary approach to the primary efficacy endpoint, the stratification factor Baseline corticosteroid use will be dropped from the CMH model in the analysis of all categorical variables.

Has been changed to read:

8.1.4.1 Primary Efficacy Variables

The primary efficacy endpoint for the Induction Study is:

Proportion of subjects achieving clinical remission (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8.

The primary efficacy endpoint for the Maintenance Study is:

Proportion of Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of ≥ 3 points and ≥ 30% from Baseline Plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) achieving clinical remission (per Full Mayo score) at Week 52.

The primary endpoint for the Induction Study will be analyzed similarly as the main study using the I-ITT1 and J-ITT1 sets. The difference between the treatment groups in the proportion of subjects achieving clinical remission at Week 8 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and Baseline

corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 8 will be classified as "no clinical remission" (non-responder imputation [NRI] method). Subjects with missing Mayo score data for Week 8 will also be classified as Week 8 non-responders.

As sensitivity analyses, logistic regression including treatment, the randomization stratification factors and additional clinically important factors such as Immunosuppressant use at Baseline, Baseline hs-CRP, and disease severity at Baseline will also be performed for the primary endpoint for the Induction Study.

For primary analysis of the Maintenance Study will compare the Week 8 responders (per Full Mayo Score) in the eow regimen versus the subjects in the ew regimen in the I-ITT2 and J-ITT2 analysis sets. The difference between the treatment regimen in the proportion of subjects achieving clinical remission at Week 52 will be assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for Induction treatment regimen and the remitter status (per Full Mayo Score) at Week 8. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. Breslow-Day test for homogeneity of odds ratios will be performed as well. Subjects with missing primary endpoint data at Week 52 will be classified as "no clinical remission" (non-responder imputation [NRI] method) for the Week 52 endpoint. Subjects with missing Mayo score data for Week 52 will also be classified as Week 52 non-responders.

Appendix K. Japan Sub-Study
Section 8.1.4.2 Secondary Efficacy Variables
Previously read:

The analysis for secondary efficacy variables will be performed similarly as the main study using the I-ITT set and the J-ITT set for endpoints at Week 8, or the I-ITT-M set and the J-ITT-M set for endpoints at Week 52, where appropriate.

Has been changed to read:

The analysis for secondary efficacy variables will be performed similarly as the main study using the I-ITT1 set and the J-ITT1 set for Induction Study endpoints at Week 8, or the I-ITT2 set and the J-ITT2 set for Maintenance Study endpoints at Week 52, where appropriate.

Appendix K. Japan Sub-Study
Section 8.1.7 Interim Analysis
Previously read:

An interim analysis of the primary endpoint and ranked secondary efficacy variables for Week 8 only as well as safety data collected from Baseline through double-blind Week 8 will be performed after the last subject enrolled in both main (ITT) and Japan sub-study ITT (J-ITT) population completes the 8-week double-blind period of the study. The analyses will be applied to integrated ITT (I-ITT) population and Japan ITT (J-ITT) population. A database lock will be performed and any discrepant data will be clarified before the lock.

Has been changed to read:

An interim analysis of the primary endpoint and ranked secondary efficacy variables for Week 8 only as well as safety data collected from Baseline through double-blind Week 8 will be performed only if performed for the main study.

Appendix K. Japan Sub-Study
Section 8.2 Determination of Sample Size of Japan Sub-study
First paragraph previously read:

Section 8.2 of the main study outlines the rationale for the sample size of 525 subjects. An additional 80 subjects has been determined as the proper sample size for the Japan sub-study based on the following rationale.

Has been changed to read:

Section 8.2 of the main study outlines the rationale for the sample size of 840 subjects. An additional 100 subjects has been determined as the proper sample size for the Japan sub-study based on the following rationale.

Appendix K. Japan Sub-Study
Section 8.2 Determination of Sample Size of Japan Sub-study
Third, fourth and fifth bullet previously read:

- Overall response rate for induction treatment at Week 8: 60%
- α = 5%, power = 95% for induction phase
- α = 5%, power = 80% for maintenance phase

Has been changed to read:

- Overall response rate for induction treatment at Week 8: 50%
- α = 5%, power = 95% for induction study
- α = 5%, power = 90% for maintenance study

Appendix K. Japan Sub-Study
Section 8.2 Determination of Sample Size of Japan Sub-study
Last paragraph, first sentence previously read:

The precisions of point estimations of remission rates in Japanese population are included within the 95% CI of remission rates in integrated population will be within 20% with 80 subjects.

Has been changed to read:

The precisions of point estimations of remission rates in Japanese population are included within the 95% CI of remission rates in integrated population will be within 20% with 100 subjects.

Appendix K. Japan Sub-Study
Section 8.3 Randomization Methods
First paragraph, third sentence previously read:

At the conclusion of the 8-week Induction Period, all subjects will be re-randomized into the 44-week Maintenance Period.

Has been changed to read:

At the conclusion of the 8-week Induction Study, all subjects will be re-randomized into the 44-week Maintenance Study.

Appendix K. Japan Sub-Study
Section 8.3 Randomization Methods
First paragraph, last sentence previously read:

All subjects will be randomized into one of two blinded treatment arms in a 1:1 ratio:

Has been changed to read:

All subjects will be randomized into one of two blinded treatment regimens in a 1:1 ratio: