1.0 Title Page

Clinical Study Protocol M13-740

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Immunomodulators or Anti-TNF Therapy

Incorporating Administrative Changes 1 and 2 and Amendments 1, 2, 3, 4 and 5

AbbVie Investigational Product:	ABT-494
Date:	07 November 2016
Development Phase:	2
Study Design:	A randomized, double-blind, placebo-controlled, multicenter study of multiple doses of ABT-494 in subjects with moderately to severely active Crohn's disease.
EudraCT Number:	2014-003240-12
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	For EU Member States: AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany For non-EU Member States: AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Contact:	[redacted]

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 October 2014
Protocol Amendment 1	19 February 2015
Administrative Change 1	12 March 2015
Protocol Amendment 2	20 October 2015
Administrative Change 2	03 December 2015
Protocol Amendment 3	05 February 2016
Protocol Amendment 4	15 April 2016

The purpose of this amendment is to:

- Section 5.1, Overall Study Design and Plan: Description, 36-Week Extension Phase, Follow-up Period: Updated the window for subject rollover to the Open Label Extension study to allow for extension on a case by case basis after consultation with the medical monitor.

  Rationale: *To allow for subjects who are eligible for the Open Label Extension study because administrative and/or logistical challenges precludes rollover within the previously allotted 10 day period.*
- Section 5.2.3.1, Prior Therapy, second paragraph: Clarify that immunosuppressants taken by subjects who inadequately responded to or were intolerant to immunomodulators should be documented beyond the 90 days.

  Rationale: *To ensure appropriate documentation of immunosuppressants use prior to study entry which is important information taken into consideration when analyzing study results.*
- Section 8.1, Statistical and Analysis Plans: Update the timing of the second interim analysis for the double-blind extension phase from when 50% of subjects who were re-randomized at Week 16 complete Week 32 – to when 100% of subjects who were re-randomized at Week 16 complete Week 36.

Rationale: *To update the timing from Week 32 to Week 36 as there is no Week 32 study visit, and to ensure sufficient sample size for robust interim analyses of the extension phase.*

- Section 5.2.1, Inclusion Criteria 9 and 10; Section 5.2.4, Contraceptive Recommendations: Clarify the duration of required contraception for females of childbearing potential, and for male subjects who are sexually active with female partner(s) of childbearing potential receiving ABT-494 to be 30 days after last dose of study drug.

  Rationale: *To ensure an adequate period of contraception after the last dose of study drug based on the ABT-494 pharmacokinetic characteristics, being non-genotoxic, no testicular findings in chronic animal toxicology studies and had no impact on male or female fertility.*

- Section 5.2.1, Inclusion Criteria 9; Section 5.2.4, Contraceptive Recommendations: Clarify the duration of required contraception for male subjects who are sexually active with female partner(s) of childbearing potential receiving ABT-494 for concomitant methotrexate to follow local approved label.

  Rationale: *To ensure that the contraception requirements while non-study drug concomitant medication is used after study completion are followed based on the local approved label.*

- Section 5.2.4, Contraceptive Recommendations, Contraception Recommendation for Males; Section 6.1.6, Pregnancy: Correct the length of post-study allowance for donation of sperm from 90 to 30 days after study end.

  Rationale: *To ensure an adequate period after study end before sperm donation because ABT-494 is not considered to be non-genotoxic, has no testicular findings in chronic animal toxicology studies and had no impact on male or female fertility.*

- Section 5.2.4, Contraceptive Recommendations, Contraception Recommendation for Males: Correct the requirement for male subject condom use and female partner using at least one contraceptive measure OR true abstinence, and not both.

  Rationale: *To correct a typographical error, as the two options are mutually exclusive.*

- Section 5.3.1.6, Collection of Samples for Gene Expression, and Section 5.3.6.3, Gene Expression Variables: Update the number of subjects participating in the Gene Expression testing to 80.

  Rationale: *To maintain the originally planned sample size for robust analyses, accounting for subject drop out, even stratification, and inadequate samples.*

- Section 6.1.3, Relationship to Study Drug: To update the definitions of "reasonable possibility" and "no reasonable possibility" that are used by the investigator to assess the relationship of an adverse event to the use of the study drug.

  Rationale: *To Updated protocol template language and parameters that need to be assessed when available, for determining relationship to study drug.*

- Section 9.1, Independent Ethics Committee (IEC) or Institutional Review Board (IRB): To clarify that an investigator will be required to submit, maintain and archive study essential documents according all other applicable regulatory requirements in addition to ICH GCP.

  Rationale: *Clarification.*

- Section 10.1, Source Documents: To clarify that the Investigator Awareness Date data point required for eCRF completion can be entered directly in the SAE eCRF and the CRF page can be considered the source for this data point.

  Rationale: *Clarification.*

- Section 13.0, Completion of the Study: To clarify that the investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements.

  Rationale: *Clarification.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-740
Name of Study Drug: ABT-494	**Phase of Development:** 2
Name of Active Ingredient: ABT-494	**Date of Protocol Synopsis:** 07 November 2016
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Immunomodulators or Anti-TNF Therapy	
Objectives: The objectives of this study are to determine the efficacy and safety of multiple doses of ABT-494 versus placebo and to assess the pharmacokinetics (PK) of ABT-494 following oral administration in subjects with moderately to severely active Crohn's Disease with a history of inadequate response to or intolerance to immunomodulators or anti-TNF therapy.	
Investigators: Multicenter	
Study Sites: Approximately 165 sites worldwide.	
Study Population: Males and females ≥ 18 and ≤ 75 years of age with a diagnosis of moderately to severely active Crohn's disease and evidence of mucosal inflammation.	
Number of Subjects to be Enrolled: Approximately 210 subjects worldwide.	
Methodology: This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and PK of ABT-494 as induction therapy in subjects with moderately to severely active Crohn's disease with a history of inadequate response to or intolerance to immunomodulators or anti-TNF therapy. The study will allow enrollment of up to 30% of subjects with primary non-response to prior anti-TNF treatment. Approximately 210 adult subjects with moderately to severely active Crohn's disease, with evidence of mucosal inflammation, defined by: • SES-CD ≥ 6, (or SES-CD ≥ 4 for patients with disease limited to the ileum), and • CDAI ≥ 220 and ≤ 450, and • Average daily liquid/soft stool frequency ≥ 2.5 or average daily abdominal pain score ≥ 2.0. Will be enrolled at approximately 165 sites worldwide. SES-CD score will be confirmed by a central reader. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized in a 1:1:1:1:1:1 ratio to receive one of the six treatment groups (double-blind ABT-494 induction doses or matching placebo). The following are the treatment groups: Group 1: ABT-494 3 mg BID Group 2: ABT-494 6 mg BID Group 3: ABT-494 12 mg BID Group 4: ABT-494 24 mg BID Group 5: ABT-494 24 mg QD Group 6: Placebo	

Methodology (Continued):

The randomization at Baseline will be stratified by endoscopic disease severity (SES-CD < 15 and ≥ 15) prior anti-TNF use (naïve and experienced) and by participation in the substudy of the gene expression in intestinal biopsies (Yes and No). As part of the randomization at Baseline, subjects will be randomly assigned (1:1) to have their follow-up ileocolonoscopy done at Week 12 or Week 16.

At Week 16, all subjects will be re-randomized into a 36-week extension phase in a ratio of 1:1:1 to one of three double-blind doses of ABT-494 (3 mg BID, 6 mg BID or 12 mg BID). The re-randomization will be stratified by the induction dose received during the first 16 weeks and overall response status (responder versus non-responder) at Week 16. The subjects who were re-randomized at Week 16 to ABT-494 24 mg QD prior to Protocol Amendment 2 will continue to receive the same double-blind dose until Week 52/PD.

Overall response consists of both Endoscopic response and Clinical response. The central reader endoscopic score will be used for calculating the Endoscopic response for the evaluation of the efficacy endpoints. However, for stratification re-randomization, the endoscopic score at baseline from central reader and the endoscopic score at Week 12 or Week 16 from site local reader will be used in order to determine response status.

Subjects will be expected to remain on blinded therapy throughout the 36 weeks extension phase. Subjects who are considered by the investigator to have not achieved meaningful symptomatic relief and meet the criteria for inadequate response at or after Week 20 will be eligible to receive open-label therapy with ABT-494 12 mg BID. Subjects who were re-randomized at Week 16 prior to Protocol Amendment 2 and are taking open-label ABT-494 24 mg QD will be transitioned to ABT-494 12 mg BID.

Subjects who continue to meet the criteria for inadequate response following a 4-week course of open-label ABT-494 12 mg BID, will be eligible to dose escalate to open-label ABT-494 24 mg BID.

Subjects with persistent inadequate response while on ABT-494 12 mg BID or 24 mg BID may be withdrawn from the study at the investigator's discretion.

Criteria for inadequate response is as follows:

- Average daily liquid/soft Stool Frequency > 2.2 OR average daily Abdominal Pain score > 1.8, AND
- An increase level of hs-CRP of at least 1 mg/L from Baseline or hs-CRP ≥ 5 mg/L, either at the previous visit or at the current visit.

Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.

In the open-label period, if a subject treated with ABT-494 24 mg BID has an occurrence of an adverse event thought to be possibly related to study medication that in the opinion of the investigator warrants dose reduction, then the dose can be de-escalated to ABT-494 12 mg BID at the investigator's discretion.

Note: Dose escalation and de-escalation are permitted only once during the study.

The duration of the study could be up to 60 weeks, including a Screening Period (35 days), a 16-week double-blind induction period, a 36-week double-blind extension phase and a 30-day follow-up period.

Visits for clinical evaluation will occur at Baseline, Weeks 2, 4, 8, 12, 16, 20, 28, 36, 44 and 52/Early Termination. An electronic diary will be dispensed at the Screening Visit. At each Study Visit, routine physical examination including evaluation of extra intestinal manifestations, average daily abdominal pain score, average daily liquid/soft Stool Frequency, fistula counts, CDAI calculation, diary review, and laboratory, adverse event, concomitant medication and vital sign assessments will be collected.

Methodology (Continued):

In addition, the following will be conducted during the study as noted below:

- Results of QoL and work productivity questionnaires (IBDQ, EQ-5D, WPAI) at Baseline, Week 8, and Weeks 16, and 52/Early Termination.
- Serum for measurement of ABT-494 concentrations at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 28, Week 36, Week 44 and Week 52/Early Termination.
- A serum pharmacodynamics sample will be drawn at Baseline, Week 8, Week 16 and Week 52/Early Termination.
- Endoscopic evaluations using SES-CD, confirmed by central reader, will be done during Screening, Week 12 or Week 16, and Week 52/Early Termination. The Week 12 or Week 16 endoscopy will not be performed if a subject discontinues the study prior to Week 8. In addition, if a subject prematurely discontinues from the extension phase of the study before or at Week 28, the endoscopy at the Early Termination Visit will not be required. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed during the same time points as the endoscopy specified above.
- Stool samples for measurement of fecal calprotectin during Screening, Week 4, Week 16, Week 28 and Week 52/Early Termination Visit and at Unscheduled Visits resulting in dose change.
- Results of Abdominal Pain Rating Scale (0 – 10 scale) evaluating Abdominal Pain Intensity will be collected at Baseline, Week 12 and Week 16. (Note: this is an additional pain scale to the daily pain assessment that is collected as part of the CDAI).
- An optional serum for evaluation of biomarkers at Baseline and Week 16.
- An optional whole blood mRNA sample will be drawn at Baseline and Week 16.
- An optional whole blood pharmacogenetic sample will be drawn at Baseline.
- An optional biopsy for Gene expression sub-study will be collected during colonoscopy at/during Screening, and at Week 12/16 for approximately 80 subjects in the study.

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

- Starting at Week 2, subjects who are taking corticosteroids at Baseline must have their steroid dose tapered.
- Aminosalicylates dose must remain unchanged for the entire study period.
- MTX dose must remain unchanged for the entire study period.
- Crohn's disease related antibiotics must remain unchanged during the induction period, except in cases of treatment related toxicity or concerns about development of antibiotic resistance.
- If a subject should experience an inadequate response during the corticosteroid taper, the subject may have their corticosteroid dose increased, per the investigator's discretion, up to and beyond the dose used at Baseline.

Note: Subjects in whom the maximum steroid dose exceeds the dose used at Baseline will be considered non-responders and will be censored for efficacy assessments from that point forward through the end of the study. These subjects will continue to be evaluated in the safety population.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female ≥ 18 and ≤ 75 years of age at Baseline.
2. Diagnosis of ileal, colonic, or ileocolonic Crohn's disease for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening Period or endoscopy performed within 15 days of the Screening Visit. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Average daily liquid/very soft stool frequency score ≥ 2.5 or average daily abdominal pain score ≥ 2.0.
4. CDAI ≥ 220 and ≤ 450.
5. Simplified Endoscopic Score for Crohn's disease (SES-CD) ≥ 6 (or ≥ 4 for subjects with disease limited to the ileum), confirmed by a central reader.
   - A video-recorded ileocolonoscopy performed within 15 days prior to Screening can be used for the local and central reader assessment.
6. Subject has inadequately responded to or experienced intolerance to previous treatment with immunomodulators (e.g., azathioprine, 6-mercaptopurine, or methotrexate) and/or an anti-TNF agent (e.g., infliximab, adalimumab, or certolizumab pegol). The clinical measures that defined inadequate response should be based on the physician/investigator clinical assessment.

   Note: Criteria for inadequate response to or experienced intolerance to previous treatment with immunomodulator or an anti-TNF agent defined as:

   - Signs and symptoms of persistently active disease despite a history induction regimen with one of the following agents:
     - At least a consecutive 90-day course of azathioprine, 6-mercaptopurine 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 or higher 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.
     - At least one 6-week induction with Infliximab: 5 mg/kg IV, 3 doses at least 2 weeks apart
     - At least one 4-week induction with Adalimumab: one 160 mg SC dose (or 80 mg SC dose in approved countries) followed by one 80 mg SC dose (or 40 mg SC dose in approved countries) followed by one 40 mg dose at least 2 weeks apart
     - At least one 4-week induction with Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart **OR**
   - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) **OR**
   - History of intolerance of at least one TNF antagonist (including, but not limited to infusion related reaction, demyelination, congestive heart failure and infection)
7. 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 anti-TB prophylaxis, prior to Baseline.

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

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis (UC), collagenous colitis or indeterminate colitis.
2. Subject with previous exposure to JAK inhibitor (e.g., tofacitinib, baricitinib).
3. Subjects who discontinued biologic therapy such as Infliximab (REMICADE), Certolizumab pegol (CIMZIA), Adalimumab (HUMIRA), Vedolizumab (ENTYVIO), Natalizumab (TYSABRI) < 8 weeks prior to Baseline. Subjects who discontinued Ustekinumab (Stelara®) less than 12 weeks prior to Baseline.
4. Subject received azathioprine or 6-mercaptopurine (6-MP) within 10 days of Baseline.
5. Subject who previously or currently use oral aminosalicylates or MTX and meets one of the following criteria:
   - Has not been on stable doses for at least 14 days prior to Baseline; or
   - Has discontinued use of aminosalicylates or MTX within 14 days of Baseline.
6. Subject who previously or currently use oral corticosteroid and meets one of the following criteria:
   - Is receiving prednisone or prednisone equivalent > 30 mg/day within 7 days of Baseline;
   - Is receiving budesonide > 9 mg/day within 7 days of Baseline;
   - Has discontinued use of corticosteroid within 7 days of Baseline;
   - Has not been on stable doses of corticosteroid for at least 7 days prior to Baseline; or
   - Has been taking both oral budesonide and prednisone (or equivalent) simultaneously.
7. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
8. Subject on probiotics who has not been on stable dose for at least 14 days prior to Baseline.
9. Subject who previously or currently use Crohn's disease related antibiotics and meets one of the following criteria:
   - Has not been on stable doses for at least 14 days prior to Baseline;
   - Has discontinued Crohn's disease related antibiotics within 14 days of Baseline.
10. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
11. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to Screening and/or during the Screening Period.
12. Subject who has had surgical bowel resection within the past 6 months or is planning any resection while enrolled in the study.
13. Subject with an ostomy, ileoanal pouch or symptomatic bowel stricture.
14. Subject with an abdominal or peri-anal abscess.
15. Subject who has short bowel syndrome.
16. Subject who previously received stem cell transplantation or Subject who previously received fecal microbial transplantation in the past 1 month.
17. Subject who received non-steroidal anti-inflammatory drugs (NSAIDs) (except topical NSAIDs and the use of low dose aspirin for cardiovascular (CV) protection) within 14 days prior to Screening and during the Screening Visit.

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

Main Exclusion (Continued):

18. 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.
19. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study.
20. Subject with positive Clostridium difficile (*C. difficile*) toxin stool assay during the Screening Period.
21. Screening laboratory and other analyses show any of the following abnormal results:
    - Serum Aspartate Transaminase (AST) or Alanine transaminase (ALT) > 1.5 × upper limit of the reference range (ULN);
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m^2;
    - Total White Blood Cell (WBC) count < 3,000/µL;
    - Absolute neutrophil count (ANC) < 1,200/µL;
    - Platelet count < 100,000/µL;
    - Absolute lymphocytes count < 750/µL;
    - Hemoglobin < 9 g/dL.
22. Any active or recurrent viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study, including recurrent/disseminated herpes zoster or known history of human immunodeficiency virus (HIV).
23. Hepatitis B (HBs Ag positive [+] or detected sensitivity on the HBV DNA PCR qualitative test for HBc Ab positive subjects) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab).
24. Subject with any active or chronic recurring infections or untreated latent TB.
25. History of moderate to severe congestive heart failure (NYHA class III or IV), cerebrovascular accident and any other condition within 6 months, which in the opinion of the Investigator, would put the subject at risk by participation in the study.
26. Use of known strong CYP3A inhibitors (e.g., clarithromycin, conivaptan, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole, grapefruit juice) or strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) from Screening through the end of the study.
27. Receipt of any live vaccine within 1 month prior to the Screening Visit, or will require live vaccination during study participation including up to 1 month after the last dose of study drug.
28. Evidence of current colonic dysplasia, history of high grade colonic dysplasia, or history of malignancy (including of the gastrointestinal tract) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
29. Has had any uncontrolled and/or clinically significant (per Investigator's judgment) illness or has had any surgical procedure within 30 days prior to Screening.
30. Positive pregnancy test at Screening (serum) or Baseline (urine).
31. Female subjects who are breastfeeding or considering becoming pregnant during the study.
32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

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

Main Exclusion (Continued):

33. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.
34. History of clinically significant drug or alcohol abuse in the last 12 months.

Investigational Product:	ABT-494
Double-Blind Induction Doses:	ABT-494 3 mg BID ABT-494 6 mg BID ABT-494 12 mg BID ABT-494 24 mg BID ABT-494 24 mg QD
Double-Blind Extension Period Doses:	ABT-494 3 mg BID ABT-494 6 mg BID ABT-494 12 mg BID ABT-494 24 mg QD
Open-Label Extension Period Doses:	ABT-494 12 mg BID ABT-494 24 mg BID
Mode of Administration:	Oral
Reference Therapy:	Matching Placebo
Doses:	N/A
Mode of Administration:	Oral

Duration of Treatment: 52 weeks

The study will include a Screening Period of up to 35 days and a double-blind induction period of 16 weeks and an extension phase of 36 weeks.

A 30-day follow-up visit will be completed for all subjects who complete the study or discontinue from the study prematurely.

Criteria for Evaluation:

Endpoint Definitions:

The following definitions apply to the efficacy variables described below:

- **Remission:** Endoscopic remission AND Clinical remission
- **Response:** Endoscopic response AND Clinical response
- **Endoscopic remission:** SES-CD ≤ 4 and at least two point reduction versus baseline and no subscore > 1 in any individual variable
- **Endoscopic response:** SES-CD at least 25% reduction from baseline
- **Clinical remission:** average daily stool frequency ≤ 1.5 and not worse than baseline AND average daily abdominal pain ≤ 1.0 and not worse than baseline
- **Clinical response:** average daily stool frequency at least 30% reduction from baseline and average daily abdominal pain not worse than baseline OR average daily abdominal pain at least 30% reduction from baseline and average daily stool frequency not worse than baseline

Criteria for Evaluation (Continued):

Efficacy:

The co-primary endpoints are:

- Proportion of subjects who achieve endoscopic remission at Week 12/16.
- Proportion of subjects who achieve clinical remission at Week 16.

The secondary endpoints *(Double-Blind Induction Treatment Period)* include:

- Proportion of subjects who achieve CDAI < 150 at Week 16.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline at Week 16.
- Proportion of subjects who achieve clinical remission at Week 12.
- Proportion of subjects who achieve remission at Week 16 (endoscopic remission at Week 12/16 and clinical remission at Week 16).
- Proportion of subjects who achieve response at Week 16 (endoscopic response at Week 12/16 and clinical response at Week 16).
- Proportion of subjects with endoscopic response at Week 12/16.
- Proportion of subjects who achieve clinical response at Week 16.
- Proportion of subjects with an average daily SF ≥ 2.5 AND average daily AP ≥ 2.0 at Baseline who achieve clinical remission at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve CDAI < 150 at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 12/16 and clinical remission at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 12/16.
- Change from Baseline in fecal calprotectin level at Week 16.
- Change from Baseline in hs-CRP at Week 16.
- Change in IBDQ from Baseline at Week 16.
- Proportion of subjects with isolated ileal Crohn's disease who achieve remission at Week 16.

Criteria for Evaluation (Continued):

Efficacy (Continued):

The secondary endpoints (Double-Blind Extension Phase) include:

- Proportion of subject who achieve remission at Week 52.
- Proportion of subjects who achieve endoscopic remission at Week 52.
- Proportion of subjects who achieve clinical remission at Week 52.
- Proportion of subject who achieve response at Week 52.
- Proportion of subjects who achieve endoscopic response at Week 52.
- Proportion of subjects who achieve clinical response at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieved CDAI < 150 at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve remission at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 52.
- Proportion of subjects who achieve CDAI < 150 at Week 52.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline at Week 52.
- Change from Baseline in fecal calprotectin level at Week 52.
- Change from Baseline in hs-CRP at Week 52.
- Change in IBDQ from Baseline at Week 52.
- Proportion of subjects with isolated ileal Crohn's disease who achieve remission at Week 52.
- Change in EIMs from Baseline at Week 52.

Additional endpoints include assessment of the above endpoints over time.

Pharmacokinetic:

Blood samples will be collected for measurement of ABT-494 plasma concentration at Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 28, Week 36, Week 44 and Week 52/Early Termination.

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, electrocardiogram, physical examination results, and clinical laboratory data will be assessed.

Statistical Methods:

Efficacy:

A total of 210 subjects will be equally allocated to five treatment groups and the placebo group, representing a randomization ratio of 1:1:1:1:1:1. The sample size for this study is based on the expected proportion of subjects who achieve endoscopic remission at Week 12/16 and on the expected proportion of subjects who achieve clinical remission at Week 16. Assuming an endoscopic remission (as well as clinical remission) rate of 12% in the placebo arm and maximum of 35% in at least one of the ABT-494 BID treatment arms (3 mg BID, 6 mg BID, 12 mg BID and 24 mg BID) at Week 12/16, a sample size of 35 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest (e.g., the minimum effective dose, MED) via modeling using MCP-Mod (Multiple comparison procedure and modeling) approach. This approach provides at least 80% average power to detect a dose effect at 5% level of significance (one-sided) with the linear, E_{max}, exponential, logistic and sigEmax models pre-specified as likely candidates to characterize the dose-response for ABT-494 for the two co-primary endpoints of clinical and endoscopic remission. Efficacy analysis will be based on all modified intended to treat subjects. The modified intent-to-treat (MITT) analysis set includes all randomized subjects who have taken at least one dose of study drug in the double-blind induction period.

The co-primary efficacy endpoints are the proportion of subjects with endoscopic remission (an SES-CD ≤ 4 and at least 2 point reduction from Baseline) and no subscore > 1 in any individual variable at Week 12/16 and the proportion of subjects with clinical remission (average daily liquid/soft stool frequency ≤ 1.5 and not worse than baseline AND average daily abdominal pain score ≤ 1.0 and not worse than baseline) at Week 16. The comparisons between an ABT-494 treatment group and placebo on the two co-primary efficacy endpoints will be performed using MCPMod approach. Subjects with missing primary endpoint data SES CD at Week 12/16 will be classified as "not achieved" (non-responder imputation [NRI] method) for the endoscopic remission endpoint. A sensitivity analysis using observed cases, which excludes those subjects with missing post-baseline endoscopy, will also be done.

The stool frequency and abdominal pain scores at an assessment visit (e.g., Week 12, Week 16) will be the average of the daily values reported during the 7 usable days preceding the scheduled assessment visit.

If 7 days daily values are not available, an average will be calculated based on the number of days with available data as follows:

- An average for the most recent 6 days will be calculated if data for only 6 days are available,
- An average for the most recent 5 days will be calculated if data for only 5 days are available,
- An average for the most recent 4 days will be calculated if data for only 4 days are available.

Statistical Methods (Continued):

Efficacy (Continued):

If the minimum number of days of diary data (i.e., 4 days for SF and AP) are not available, then the subject's score for that visit will be considered missing and NRI will be used for any endpoints (e.g., clinical remission) relating to data for this visit. Subjects who discontinue prior to Week 16 for any reason will be considered as "not-achieved" for clinical remission endpoint.

The following sensitivity analyses for the primary endpoint of clinical remission will be conducted:

- An analysis of observed cases, which excludes those subjects with missing SF or AP data at scheduled assessment visits.
- The primary analysis will be repeated using mixed-imputation. Subjects who discontinue prior to Week 16 due to lack of efficacy or adverse events will be considered as "not achieved" for the clinical remission. Subjects who discontinue for other reasons will be categorized according to LOCF.

The dose-response relationships using the most significant model in MCPMod among the five ABT-494 treatment groups and placebo group will be characterized for the primary endpoints endoscopic remission at Week 12/16 and clinical remission at Week 16. The response function will be the log odds (logit) of the proportion of subjects with endoscopic/clinical remission. The fitted curve will be shown graphically with confidence intervals for each dose. Estimates of the treatment differences in the response function and associated 95% confidences for each active dose against placebo will be calculated from the most significant model, as well as the average of all significant models. These results will be back-transformed to give point estimates of the difference in proportions and associated 95% confidence intervals.

In general, continuous secondary efficacy variables with repeated measurements will be analyzed using a Mixed Effect Repeated Measure (MMRM) model. Continuous secondary efficacy variables will also be analyzed using an Analysis of Covariance (ANCOVA) model including factors for treatment group and stratification variable, Crohn's disease severity (SES-CD < 15, ≥ 15) at Baseline and prior anti-TNF use (naïve and experienced). Baseline values will be used as a covariate in the MMRM and ANCOVA models. Categorical secondary efficacy variables will be analyzed using the CMH test controlling for stratification variables Crohn's disease severity (SES-CD < 15, ≥ 15) at Baseline and prior anti-TNF use (naïve and experienced).

Pharmacokinetics:

Individual plasma concentrations of ABT-494 will be tabulated and summarized. A non-linear mixed-effects modeling approach will be used to estimate the population central value and the empirical Bayesian estimates of the individual values for ABT-494 oral clearance (CL/F) and volume of distribution (V_{ss}/F). Additional parameters may be estimated if useful in the interpretation of the data.

Safety:

Safety analyses will be carried out using the safety population, which includes all subjects who receive at least one dose of study medication. Incidence of adverse events, changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed. Treatment-emergent adverse events will be tabulated by system organ class and by MedDRA preferred term for each treatment group for the induction treatment period, extension phase and over the entire study. Mean change from Baseline for laboratory and vital signs data will be summarized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-mercaptopurine
AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
ANC	Absolute Neutrophil Count
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood Urea Nitrogen
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CDAI	Clinical Disease Activity Index
CD4, CD8	Cluster of Differentiation
CGC	Common Gamma-Chain
CHF	Congestive Heart Failure
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
CMH	Cochran-Mantel-Haenszel
CPK	Creatine Phosphokinase
CR	Clinical Remission
CRF	Case Report Form
CRP	C-Reactive Protein
C_{trough}	Trough Plasma Concentration
CXR	Chest X-Ray
CYP3A	Cytochrome P450 3A
CYP2D6	Cytochrome P450 2D6
DM	Diabetes Mellitus
DMARD	Disease-Modifying Anti-Rheumatic Drug

DMC	Independent Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIM	Extra-Intestinal Manifestations
EQ-5D	EuroQoL-5D
ET	Early termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
gp130	Glycoprotein 130
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
Hbs Ab	Hepatitis B surface antibodies
Hbs Ag	Hepatitis B surface antigen
HCV Ab	Hepatitis C Virus Antibody
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
hsCRP	High-Sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
JAK	Janus Activated Kinase
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Repeated Measure
MTX	Methotrexate
NK	Natural Killer Cells
NOAEL	No Observable Adverse Effect Level
NRI	Non-Responder Imputation
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OC	Observed Cases
PE	Physical Examination
PG	Pharmacogenetic
PK	Pharmacokinetic
PPD	Purified Protein Derivative
QTc	QT Interval Corrected for Heart Rate
QTcF	QT Interval Corrected for Heart Rate by Fridericia's Formula
RA	Rheumatoid Arthritis
RAVE®	EDC System from Medidata
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SDP	Study designated physician
SES-CD	Simplified Endoscopic Score for Crohn's Disease
SFPS	CDAI components "Number of liquid or very soft stools" and "Abdominal pain" (Stool [liquid/soft] Frequency + Abdominal Pain Score; SFPS)
SGOT/AST	Serum Glutamic-Oxaloacetic Transaminase/Aspartate Transaminase
SGPT/ALT	Serum Glutamic-Pyruvic Transaminase/Alanine Transaminase
STAT	Signal Transduction Activators of Transcription
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to Maximum Observed Plasma Concentration
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
Tyk2	Tyrosine Kinase 2
UC	Ulcerative Colitis
ULN	Upper Limit of Normal

WBC	White Blood cell Count
WPAI	Work Productivity and Impairment Questionnaire

2.0 Table of Contents

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3.0 Introduction

Crohn's disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally granulomatous inflammation that can affect any segment of the gastrointestinal tract.[1] The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups.[2,3] In North America, the incidence of CD is estimated to be 3.1 to 14.6 cases per 100,000 persons. Prevalence rates range from 26 to 99 cases per 100,000 persons. In Europe, CD has an incidence of 0.7 to 9.8 cases per 100,000 persons and a prevalence of 8.3 to 214 cases per 100,000 persons.[2]

CD has been characterized as a progressive disease that leads to complications. In a population based study from southeastern Norway, a substantial number of patients demonstrated a stricturing or penetrating phenotype at 10 years after diagnosis.[4] Moreover, approximately 80% of patients diagnosed with CD will require at least one surgery related to the disease at some point in time.[5]

Given that no known medical or surgical cure currently exists for CD, the therapeutic strategy is to reduce symptoms, improve quality of life, reduce endoscopic evidence of inflammation, and minimize short- and long-term toxicity and complications.[6] Currently, patients with moderate to severe disease are usually treated with conventional pharmacologic interventions, which include corticosteroids and immunomodulatory agents such as azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX).[1,7] However, the use of these agents is limited by slow onset of action (3 to 6 months) and sub-optimal efficacy in early disease and in more severe patients.[8,9] The potential risks from long-term use of corticosteroids are well-known. Adverse events (AEs) associated with short-term use of corticosteroids include acne, moon face, edema, skin striae, glucose intolerance, and sleep/mood disturbances; potential AEs observed with longer term use (usually 12 weeks or longer but sometimes shorter durations) include posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy, and

susceptibility to infection.[10,11] The safety risks for AZA and 6-MP include pancreatitis, bone marrow depression, infectious complications, and malignant neoplasms.[12] MTX may be associated with bone marrow depression and liver and pulmonary toxicity. Patients who do not respond to conventional therapies may be treated with biologics, such as anti-TNF α therapies.[1,7] Potential risks with anti-TNF α include infusion or injection site reactions, serious infections, lymphoma, heart failure, lupus-like syndromes, and demyelinating conditions.[12] Despite the beneficial results achieved with the available anti-TNF α agents, approximately 40% of patients who receive them for the first time do not have a clinically meaningful response (primary non-responders).[13-17] Among patients who initially respond and continue to receive maintenance treatment for longer durations, approximately 38% become non-responders after 6 months and approximately 50% become non-responders at 1 year (secondary non-responders).[14,16] Patients who initially respond to a first anti-TNF agent but then lose response tend to have lower response and remission rates to the second anti-TNF agent.[16,18] A new class of biologics, anti-integrin antibodies, has been studied in patients with prior anti-TNF use. Natalizumab, a humanized monoclonal antibody to α4β1 and α4β7 integrins, showed promise for patients with prior exposure to anti-TNF-α therapy; more than half of the patients had a response to the induction regimen.[19] However, natalizumab's use after approval in 2008 has been severely limited due to the serious risk for progressive multifocal leukoencephalopathy (PML) attributed to activation of the latent JC virus.[20] Clearly, the medical need for additional therapeutic options in CD for patients with inadequate response to or intolerance to conventional therapies and anti-TNF α agents remains.

Targeting the JAK (Janus activated kinase) signaling pathway for autoimmune diseases, such as RA and CD, is well-supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. The activation of the JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders.[21]

Although the pathogenesis of CD is not completely understood, the imbalance between anti-inflammatory and pro-inflammatory cytokines in the mucosal immune system is thought to play an important role in CD. Cells from the innate mucosal immune system, i.e., TH1 or TH17, are over-activated and secrete various pro-inflammatory cytokines such as interferon (INF)-g, TNFα, interleukin IL-6, IL-1b, IL-12, IL-23. These cytokines signal via JAK pathways.[22]

The JAK comprise 4 family members: JAK1, 2, 3, and Tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases transduce cytokine-mediated signals, and are associated with membrane cytokine receptors such as common gamma-chain (CGC) receptors and the glycoprotein 130 (gp130) trans-membrane proteins.[23]

JAK3 and JAK1 are components of the CGC cytokine receptor complexes and blockade of either inhibits signaling by the inflammatory cytokines IL-2, -4, -7, -9, -15 and -21.[24] Cytokines such as IL-6 bind to gp130 and transduce its signal predominantly via JAK1.[25] Targeting the IL-6 receptor (IL-6R) is a promising approach given the fact that expression of IL-6 and soluble IL-6 receptors is elevated in patients with active CD.[26] Further, a proof of concept study in patients with active CD with tocilizumab, a humanized monoclonal antibody against IL-6R, showed an encouraging clinical response.[27] Thus, inhibition of JAK1 is expected to attenuate the signaling of IL-6 and other pro-inflammatory cytokines (i.e., IFN-g), that are involved in development of CD.

ABT-494 is a novel JAK1 inhibitor being developed for the treatment of adult patients with inflammatory diseases. Based on in vitro selectivity assays and in vivo animal models, ABT-494 has demonstrated that inhibiting JAK1 with minimal impact on JAK2 is feasible at efficacious drug exposure levels. Thus, the enhanced selectivity of ABT-494 has the potential for an improved benefit/risk profile by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis. Also, the minimum of activity of ABT-494 against JAK3, which is involved in IL-15 signal transduction cascade, could potentially minimize a decrease in NK cell counts observed with tofacitinib that may have contributed to increased incidences of viral infection, particularly reactivation of herpes zoster.

The toxicology profile of ABT-494 was initially evaluated in repeat-dose 4-week studies in rats and dogs, and the dog has been identified as the most sensitive species. Adverse findings in dogs included dose-related decreases in hemoglobin and red cell mass (red blood cell counts, hemoglobin concentration, hematocrit) and microscopic findings in popliteal lymph nodes (mixed cell infiltrates with extension into pericapsular tissues) in animals administered 3 or 5 mg/kg/day ABT-494. However, there were no changes observed for these nodes on physical exam and no systemic manifestation of this finding or evidence of this at other lymph node sites or organs.

In a 4-week toxicity study in rats, mild decreases in red blood cell counts and hemoglobin and non-adverse, dose-dependent decreases in circulating lymphocytes were observed, both effects being reversible. In rats, discolored urine, either brown or black, was observed at high doses. While this was not observed at the end of the recovery period at any dose, the significance of this observation is not known as no correlating histopathologic findings were identified. At a very high dose of 100 mg/kg/day of ABT-494 in rats, the adverse findings included mortality as well as tubular degeneration/regeneration in the kidney and liver necrosis.

Subsequent longer chronic toxicity studies in dogs (9 months) and rats (6 months) have confirmed the earlier findings in both species. In the 9-month toxicity study in dogs, ABT-494 was administered at 0.1, 0.5, and 1.5 mg/kg/day. There were no adverse findings at any dose group, and the overall results confirmed the earlier 4-week study findings, with mixed cell infiltration in interdigital skin of paws and draining lymph nodes which was considered secondary to ABT-494 related immune modulation. There was only a mild decrease (not adverse) in red cell mass at 0.5 and 1.5 mg/kg/day. In the 6-month toxicity study in rats, ABT-494 was dosed up to 50 mg/kg/day and was associated with renal tubular degeneration/regeneration.

ABT-494 is currently in clinical development for the treatment of patients with rheumatoid arthritis (RA). There have been two Phase 1 studies with ABT-494. Study M13-401, a single-dose ascending dose study of ABT-494 at 1 mg up to 48 mg, has been completed. This study also looked at the effects of ketoconazole and food on the

pharmacokinetics (PK) of ABT-494. Single doses of ABT-494 were well tolerated. Plasma concentration of ABT-494 increased approximately dose proportionally in the dose range studied. Ketoconazole, a strong CYP3A inhibitor, increased ABT-494 AUC and C_{max} approximately 1.7- to 1.8-fold. Therefore, to minimize overlap in drug concentrations between dosing groups coadministration of strong CYP3A inhibitors or inducers is restricted in the present study. Food had no effect on the exposure (AUC) of ABT-494. Therefore, ABT-494 can be administered with or without food in the present study.

Study M13-540 evaluated the effects of rifampin on the PK and safety of a single dose of ABT-494 in healthy adult subjects. Preliminary results suggested that rifampin, a potent CYP3A inducer, decreased ABT-494 AUC and C_{max} approximately 2- to 2.5-fold following 8 days of rifampin administration.

Preliminary results after multiple ascending doses of ABT-494 in healthy volunteers are available from Study M13-845. The randomized, double-blind, placebo-controlled study was designed to evaluate the safety, tolerability and pharmacokinetics of ABT-494 at four dose levels of 3, 6, 12 and 24 mg BID. In each dose group, 11 subjects were randomized (8 to ABT-494 and 3 to placebo) and received study medication twice daily (BID) for 14 consecutive days. No serious or fatal adverse events or AEs leading to discontinuation were reported during the study. Treatment-emergent adverse events (TEAE) were reported in 7 (58.3%) subjects receiving placebo and in 11 (34.3%) subjects receiving ABT-494 with the overall incidence of TEAEs at 2 (25.0%), 2 (25.0%), 3 (37.5%) and 4 (50%) of subjects experienced TEAEs in the 3 mg, 6 mg, 12 mg and 24 mg dose groups, respectively. All TEAEs were considered mild (Grade 1) in severity and reported to have a reasonable possibility of being related to study drug except 2 events in one subject in the placebo group were considered as having no reasonable possibility of being related. Most common TEAE in the ABT-494 treatment groups (n = 32) were headache (15.6%), abdominal pain (6.3%), diarrhea (6.3%), and nasopharyngitis (6.3%). No clinically meaningful changes in laboratory values, vital signs or ECG findings were observed during the study.

Preliminary results indicated that at steady state, ABT-494 had minimal to no accumulation with a median T_{max} of approximately 2 hours. ABT-494 exposure was approximately dose-proportional across the dose range studied, with concentrations rapidly decreasing following T_{max} followed by an elimination phase with an apparent elimination half-life of approximately 8 to 16 hours following the last dose on Day 14. Approximately 19% to 21% of ABT-494 was excreted as unchanged parent in the urine during a dose interval in the steady state.

A detailed discussion of the preclinical toxicology, metabolism, pharmacology and safety experience with ABT-494 can be found in the current Investigator's Brochure.[28]

Rationale for Development of a JAK Inhibitor in CD

Preclinical pharmacology studies run in the mouse CD45RBhi transfer colitis model demonstrate efficacy of an AbbVie JAK inhibitor, ABT-317. In this model, CD4 + CD45Rbhi T cells are transferred into RAG-/-SCID mice. The resulting colonic inflammation has histopathological features of inflammatory bowel disease including goblet cell loss, lymphocyte/monocyte-mediated inflammation, and mucosal thickening and "cobblestone" appearance as measured by endoscopy. This model has been validated with clinical benchmarks including anti-TNF antibodies, anti-p40 (IL-12/IL-23) antibodies, and steroids. Studies performed with ABT-494 showed a trend towards efficacy in the model, but did not reach statistical significance due to variable responses across all of the animals. The in vivo pharmacology of ABT-494 is challenging to study in mice due to poor PK in this species. By contrast, ABT-317 is a JAK1-selective inhibitor, similar to ABT-494 in potency, that exhibits adequate murine PK to enable these studies. Also, ABT-317 exhibits similar efficacy to ABT-494 in preclinical RA models in rats, where pharmacokinetics enable study of both compounds. In the transfer colitis model, ABT-317 mitigates weight loss and improves both the endoscopy score and histology in treated animals relative to the vehicle controls. The efficacy observed with ABT-317 was equivalent to that observed with the anti-p40 positive control. These data support JAK blockade as a possible effective treatment for CD.

3.1 Differences Statement

This Phase 2 study differs from other ABT-494 studies as it is the first to evaluate the efficacy, safety and pharmacokinetics of ABT-494 in subjects with CD.

3.2 Benefits and Risks

CD is a chronic inflammatory condition involving the gastrointestinal tract. The disease is associated with significant morbidity (including abdominal pain, diarrhea, weight lost/malnutrition and gastrointestinal fistulas/strictures/abscesses) related to the underlying inflammation. Although newer treatments such as the anti-TNF antibodies have improved the standard of care for patients with CD, there remains significant unmet medical need for patients with inadequate or loss of response to these agents, and efforts are ongoing to develop novel therapies. This protocol will study patients who are unable to tolerate anti-TNF therapies and/or have had an insufficient response to treatment with an anti-TNF therapy. Currently these patients have limited options for treatment, and may be subjected to repeated courses of corticosteroids, which are associated with a wide ranging spectrum of toxic effects affecting multiple organ systems. Natalizumab, an antibody directed against α4 integrin, is approved for patients with inadequate response or intolerance to anti-TNF agents, but the risk of associated progressive multifocal leukoencephalopathy has greatly limited its use. Vedolizumab, a monoclonal antibody that binds to the α4β7 integrin and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue, was recently approved for adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator.

Clinical efficacy in targeting proinflammatory cytokines and downstream signaling pathways has been demonstrated in RA and may be helpful in treating patients with CD. Several JAK inhibitors demonstrated proof of concept in RA subjects.[29,30] These drugs are also being studied for the treatment of patients with inflammatory bowel disease.

The second generation of JAK inhibitors currently in development display varying potency and selectivity directed at members of the JAK family.[31] Tofacitinib is a non-selective JAK inhibitor targeting JAK1, JAK2 and JAK3, but most potently inhibits JAK3.[31] Although tofacitinib improves the clinical signs and symptoms of RA, questions remain surrounding the safety profile regarding apparent increases in the incidences of serious infection, malignancies, herpes zoster, and hematologic adverse events.

Tofacitinib has also been associated with reduced levels of hemoglobin, absolute lymphocytes counts, and total white blood cell counts in some subjects and also increased serum creatinine; total cholesterol, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C); and liver transaminases (ALT and AST).[32,34] The increases in serum creatinine, lipids, and liver transaminase values typically have been asymptomatic, reversible, and were not associated with any overt declines in renal or hepatic function.

ABT-494 is a novel JAK1 selective inhibitor with minimal inhibitory effects on JAK2 and JAK3, which could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways. We propose to initiate a Phase 2 study in CD subjects with multiple doses of ABT-494 based on the following supportive findings: 1) demonstrated improved potency of ABT-494 versus tofacitinib in preclinical models of inflammation; 2) confirmed JAK1 selectivity of ABT-494 in both preclinical and clinical settings; 3) acceptable preclinical toxicological findings in chronic toxicity studies in two species; 4) acceptable safety and tolerability profile of ABT-494 in single ascending dose (SAD) and multiple ascending dose (MAD) studies in healthy volunteers and 5) evidence that JAK inhibition in preclinical models of inflammatory bowel disease results in clinical and endoscopic improvement. The current Phase 2 Study M13-740 will assess the benefit to risk profile of ABT-494 in CD subjects who have had an insufficient clinical response to anti-TNF therapies.

ABT-494 is a potent JAK1 selective inhibition that has been associated with endoscopic improvement and healing of the intestinal mucosa in preclinical animal models. More recently, filgotinib, a JAK1 inhibitor in Phase 2 clinical development in Crohn's disease

was associated with superior clinical remission versus placebo.[33] This study included subjects who could have been inadequate responders or intolerant to either immunomodulators or anti-TNF therapies. Of note, this treatment effect was more prominent in subjects who have inadequate responders to immunomodulators only. AbbVie proposes to include this patient population to assess the effect of ABT-494 and whether they would benefit the most from such therapy.

4.0 Study Objective

The objective of this study is to determine the efficacy and safety of multiple doses of ABT-494 versus placebo and to assess the pharmacokinetics of ABT-494 following oral administration in subjects with moderately to severely active Crohn's disease with a history of inadequate response to or intolerance to immunomodulators or anti-TNF therapy.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

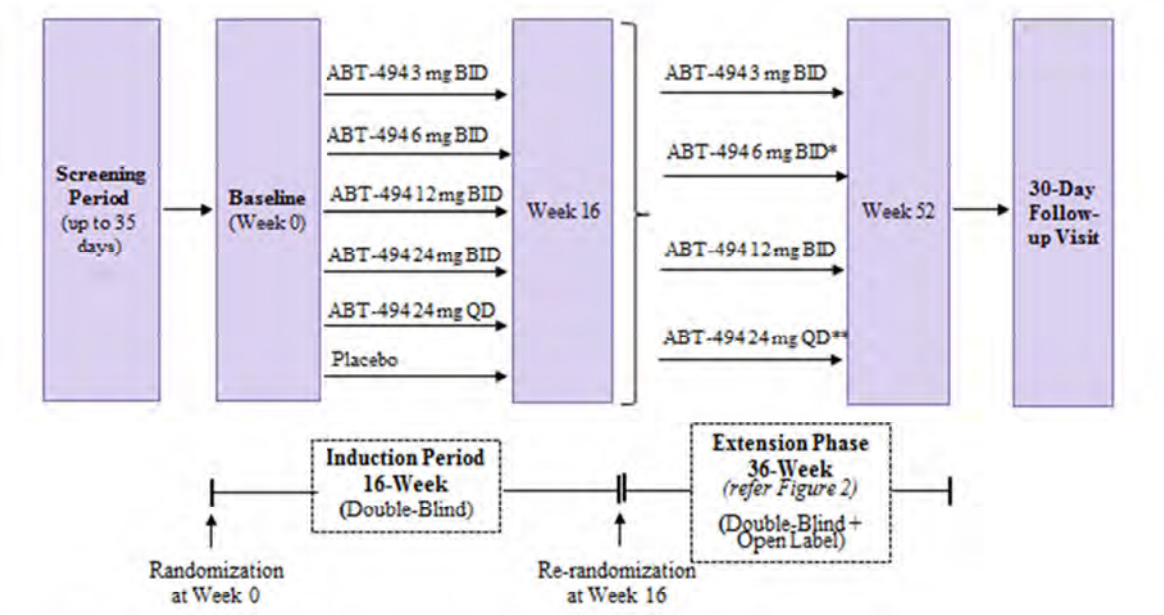
This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of ABT-494 as induction therapy in subjects with moderately to severely active Crohn's disease and evidence of mucosal inflammation defined by a SES-CD ≥ 6 (or ≥ 4 for subjects with disease limited to the ileum) and average daily soft/liquid stool frequency ≥ 2.5 or average daily abdominal pain score of ≥ 2.0; and CDAI ≥ 220 and ≤ 450, with a history of inadequate response or intolerance to immunomodulators or anti-TNF therapy. The study will allow enrollment of up to 30% of subjects who were primary non responders to anti-TNF treatment.

The study is designed to enroll 210 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target numbers of subjects have been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The study duration could be up to 60 weeks, including a Screening Period of up to 35 days, a 16-week double-blind induction period, a 36-week double-blind extension phase, and a 30-day follow-up period. Subjects who meet eligibility criteria will be randomized in a 1:1:1:1:1:1 ratio to one of the double-blinded induction treatment arms.

The schematics of the overall study design are shown in Figure 1.

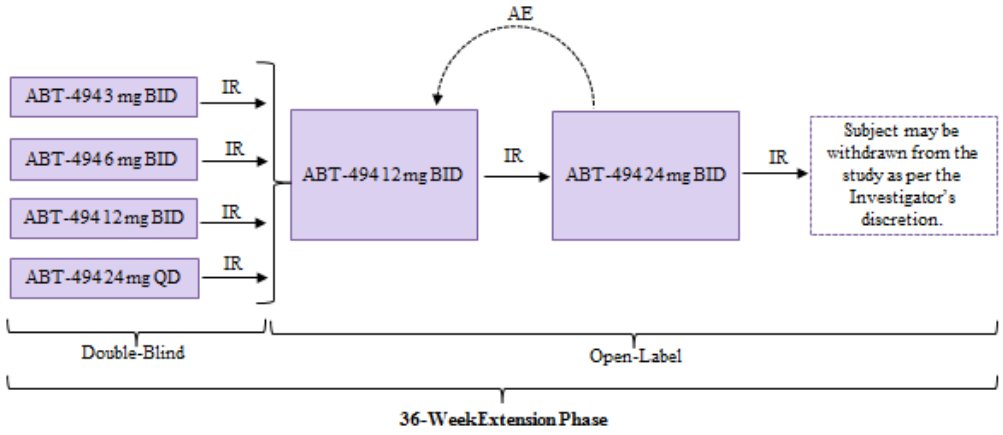
Figure 1. Study Design Schematic



*The 6 mg BID dose arm was added to replace the 24 mg QD dose arm in Protocol Amendment 2

**Subjects who were re-randomized at Week 16 to 24 mg QD prior to Protocol Amendment 2 will continue to receive the double-blind 24 mg QD dose until Week 52/PD.

Figure 2. Study Design Schematic for Open-Label Extension Option for Patients Who Do Not Adequately Respond During the Extension Phase



IR: Inadequate Response

Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures as outlined in Table 1.

An e-diary will be dispensed and training will be provided to the subject at the Screening Visit.

Laboratory tests performed during the Screening period can be repeated in case the abnormalities are considered to be transient by the investigator.

16-Week Induction Period

This period will begin at the Baseline Visit (Week 0) and will end at the Week 16 Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the

study and randomized to double-blind induction period. The randomization at Baseline will be stratified by endoscopic disease severity (SES-CD < 15 and ≥ 15), prior anti-TNF use (naïve and experienced) and by participation in the substudy of the gene expression in intestinal biopsies (Yes and No). As part of the randomization at Baseline, subject will be randomly assigned (1:1) to have their follow-up ileocolonoscopy done at Week 12 or Week 16. During this period of the study, subjects will visit the study site at Weeks 2, 4, 8, 12 and 16. A ± 3-day window is permitted around scheduled study visits. The last dose of study drug during this period is taken the evening prior to the Week 16 visit.

Subjects may discontinue study drug treatment at any time during study participation. Subjects that end study participation early will have an Early Termination (ET) Visit and complete the procedures outlined for the ET Visit in Table 1 as soon as possible after the last dose of study drug and preferably prior to the administration of any new therapies.

36-Week Extension Phase

At Week 16, subjects who have completed the induction period will be re-randomized in a ratio of 1:1:1 to one of the three double-blinded doses of ABT-494 3 mg BID, 6 mg BID or 12 mg BID. The re-randomization will be stratified by dose received during the first 16 weeks, and overall response (responder versus non-responder) at Week 16. The subjects who were re-randomized at Week 16 to ABT-494 24 mg QD prior to Protocol Amendment 2 will continue to receive the same double-blind dose until Week 52/PD.

The central reader endoscopic score will be used for calculating the Endoscopic response for the evaluation of the efficacy endpoints. However, for stratification at the time of re-randomization, the endoscopic score at BL from central reader and the endoscopic score at Week 12 or Week 16 from site local reader will be used in order to determine response status.

Clinical response is defined as average daily liquid/soft stool frequency reduction of at least 30% from Baseline and average daily abdominal pain not worse than Baseline OR

average daily abdominal pain reduction at least 30% from baseline and average daily stool frequency not worse than Baseline.

During this period of the study, subjects will visit the study site at Weeks 20, 28, 36, 44, and 52/Early Termination. A ± 3-day window is permitted around scheduled study visits. The last dose of study drug is taken the evening prior to the Week 52 visit.

Subjects will be expected to remain on double-blinded therapy throughout the entire 36-week extension phase. However, subjects who are considered by the investigator to have not achieved meaningful symptomatic relief and meet the criteria for inadequate response at or after Week 20 will be eligible to receive the open-label therapy with ABT-494 12 mg BID, Figure 2. Subjects who were re-randomized at Week 16 prior to Protocol Amendment 2 and are taking open-label ABT-494 24 mg QD will be transitioned to ABT-494 12 mg BID.

Subjects who still continue to meet criteria for inadequate response following a 4-week course of open-label ABT-494 12 mg BID will be eligible to dose escalate to open-label ABT-494 24 mg BID.

Subjects with persistent inadequate response while on ABT-494 12 mg BID or 24 mg BID may be withdrawn from the study at the investigator's discretion.

Criteria for Inadequate response are as follows:

- Average daily liquid/soft Stool Frequency > 2.2 OR average daily Abdominal Pain score > 1.8 AND
- An increase level of hs-CRP of at least 1mg/L from Baseline or a hs-CRP ≥ 5 mg/L, either at the previous visit or at the current visit.

Note: hs-CRP will be performed by Central Lab. However, for the purpose of evaluating Inadequate Response criteria, hs-CRP can also be done at local lab.

Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.

In the open-label period, if the subject treated with 24 mg BID has an occurrence of an adverse event thought to be possibly related to study medication that in the opinion of the investigator warrants dose reduction, then the dose can be de-escalated to ABT-494 12 mg BID at the investigator's discretion.

Note: Dose escalation and de-escalation are permitted only once during the study.

Subjects may discontinue study drug treatment at any time during study participation. Subjects that end study participation early will have an ET Visit and complete the procedures outlined for the ET Visit in Table 1 as soon as possible after the last dose of study drug and preferably prior to the administration of any new therapies.

Subjects who are not re-randomized at Week 16 or subjects who early terminated from the study will have a follow-up visit approximately 30 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs), and to collect vital signs and clinical laboratory tests.

Follow-Up Period

Subjects who have completed the Week 52 visit and do not enter the Open Label Extension Study (Study M14-327) will have a follow-up visit approximately 30 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs), and to collect vital signs and clinical laboratory tests.

Subjects will be evaluated for entry into the Open Label Extension at the final study visit (Week 52) of Study M13-740 or up to 10 days following the Last Visit (Week 52) of Study M13-740. The 10 day window for subject rollover may be extended on a case by case basis after consultation with the medical monitor. The Week 52 visit of Study M13-740 will be considered Week 0 (Baseline) of Open Label Extension Study.

Re-Screen

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. The subject must meet all the inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the assessment of a purified protein derivative (PPD) test (or equivalent), or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold test or T-SPOT TB test), chest x-ray, HBV, HCV 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 with biopsy 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 (from the previous screening endoscopy). All other screening procedures will be repeated. As appropriate, sites are encouraged to contact the AbbVie Medical Monitor to confirm if subjects should or should not be re-screened.

Unscheduled Visits

Unscheduled Visits are for purposes when the subject is coming in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples will be obtained for the laboratory tests listed in Table 2.

Visits for dispensing new study drug in case of temperature excursion, loss or damage are not considered an Unscheduled Visit. In addition, visits to only retest a lab will not be considered an Unscheduled Visit.

5.2 Selection of Study Population

It is anticipated that approximately 210 subjects with moderately to severely active CD who meet all of the inclusion criteria and none of the exclusion criteria will be randomized at approximately 165 study centers worldwide.

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

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

1. Male or female ≥ 18 and ≤ 75 years of age at Baseline.
2. Diagnosis of ileal, colonic, or ileocolonic Crohn's disease for ≥ 3 months prior to Baseline confirmed by endoscopy during the Screening Period or endoscopy performed within 15 days of the Screening Visit. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
3. Average daily liquid/very soft stool frequency score ≥ 2.5 or average daily abdominal pain score ≥ 2.0.
4. CDAI ≥ 220 and ≤ 450.
5. Simplified Endoscopic Score for Crohn's disease (SES-CD) ≥ 6 (or ≥ 4 for subjects with disease limited to the ileum), confirmed by a central reader.
   - A video-recorded ileocolonoscopy performed within 15 days prior to Screening can be used for the local and central reader assessment.
6. Subject has inadequately responded to or experienced intolerance to previous treatment with immunomodulators (e.g., azathioprine, 6-mercaptopurine, or methotrexate) and/or an anti TNF agent (e.g., infliximab, adalimumab, or certolizumab pegol). The clinical measures that defined inadequate response should be based on the physician/investigator clinical assessment.

   Note: Criteria for inadequate response to or experienced intolerance to previous treatment with an immunomodulator or anti-TNF agent defined as:

   - Signs and symptoms of persistently active disease despite a history of induction regimen with one of the following agents:

- At least a consecutive 90-day course of azathioprine, 6-mercaptopurine 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 or higher 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.
- At least one 6-week induction with Infliximab: 5 mg/kg IV, 3 doses at least 2 weeks apart
- At least one 4-week induction with Adalimumab: one 160 mg SC dose (or 80 mg SC dose in approved countries) followed by one 80 mg SC dose (or 40 mg SC dose in approved countries) followed by one 40 mg dose at least 2 weeks apart
- At least one 4-week induction with Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart OR
  - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) OR
  - History of intolerance of at least one TNF antagonist (including, but not limited to infusion-related reaction, demyelination, congestive heart failure and infection)

7. 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 anti-TB prophylaxis, prior to Baseline.
8. A negative serum pregnancy test for all female subjects at the Screening Visit and a negative urine pregnancy test for all female subjects of childbearing potential at baseline prior to the first dose of study drug.

9. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
10. Male subjects who are sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 30 days after the last dose of study drug to practice the protocol-specified contraception (refer to Section 5.2.4).
11. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
12. 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 and a 12-lead electrocardiogram (ECG) performed during Screening.

5.2.2 Exclusion Criteria

1. Subject with a current diagnosis of ulcerative colitis (UC), collagenous colitis or indeterminate colitis.
2. Subject with previous exposure to JAK inhibitor (e.g., tofacitinib, baricitinib).
3. Subjects who discontinued biologic therapy such as (Infliximab (REMICADE), Certolizumab (CIMZIA), Adalimumab (HUMIRA), Vedolizumab (ENTYVIO), Natalizumab (TYSABRI) < 8 weeks prior to Baseline. Subjects who discontinued Ustekinumab (Stelara®) less than 12 weeks prior to Baseline.
4. Subject received azathioprine or 6-mercaptopurine (6-MP) within 10 days of Baseline.
5. Subject who previously or currently use oral aminosalicylates or MTX and meets one of the following criteria:
   - Has not been on stable doses for at least 14 days prior to Baseline; or
   - Has discontinued use of aminosalicylates or MTX within 14 days of Baseline.

6. Subject who previously or currently use oral corticosteroid and meets one of the following criteria:
   - Is receiving prednisone or prednisone equivalent > 30 mg/day within 7 days of Baseline;
   - Is receiving budesonide > 9 mg/day within 7 days of Baseline;
   - Has discontinued use of corticosteroid within 7 days of Baseline;
   - Has not been on stable doses of corticosteroid for at least 7 days prior to Baseline; or
   - Has been taking both oral budesonide and oral prednisone (or equivalent) simultaneously.
7. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
8. Subject on probiotics who has not been on stable dose for at least 14 days prior to Baseline.
9. Subject who previously or currently use Crohn's disease related antibiotics and meets one of the following criteria:
   - Has not been on stable doses for at least 14 days prior to Baseline;
   - Has discontinued Crohn's disease related antibiotics within 14 days of Baseline.
10. Subject received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
11. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 7 days prior to Screening and/or during the Screening Period.
12. Subject who has had surgical bowel resections within the past 6 months or is planning any resection while enrolled in the study.
13. Subject with an ostomy, ileoanal pouch or symptomatic bowel stricture.
14. Subject with an abdominal or peri-anal abscess.

15. Subject who has short bowel syndrome.

16. Subject who previously received stem cell transplantation or Subject who previously received fecal microbial transplantation in the past 1 month.

17. Subject who received non-steroidal anti-inflammatory drugs (NSAIDs) (except topical NSAIDs and the use of low dose aspirin for CV protection) within 14 days prior to Screening and during the Screening Visit.

18. 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.

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

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

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

    - Serum Aspartate Transaminase (AST) or Alanine transaminase (ALT) > 1.5 × upper limit of the reference range (ULN);
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m^2;
    - Total White Blood Cell (WBC) count < 3,000/µL;
    - Absolute neutrophil count (ANC) < 1,200/µL;
    - Platelet count < 100,000/µL;
    - Absolute lymphocytes count < 750/µL;
    - Hemoglobin < 9 gm/dL.

22. Any active or recurrent viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study, including recurrent/disseminated herpes zoster or known history of human immunodeficiency virus (HIV).

23. Hepatitis B (HBs Ag positive [+] or detected sensitivity on the HBV DNA PCR qualitative test for HBc Ab positive subjects) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab).
24. Subject with active or chronic recurring infections or untreated latent TB.
25. History of moderate to severe congestive heart failure (NYHA class III or IV), cerebrovascular accident and any other condition within 6 months, which in the opinion of the Investigator, would put the subject at risk by participation in the study.
26. Use of known strong CYP3A inhibitors (e.g., clarithromycin, conivaptan, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole, grapefruit juice) or strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) from Screening through the end of the study.
27. Receipt of any live vaccine within 1 month prior to the Screening Visit, or will require live vaccination during study participation including up to 1 month after the last dose of study drug.
28. Evidence of current colonic dysplasia, history of high grade colonic dysplasia, or history of malignancy (including of the gastrointestinal tract) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
29. Has had any uncontrolled and/or clinically significant (per Investigator's judgment) illness or has had any surgical procedure within 30 days prior to Screening.
30. Positive pregnancy test at Screening (serum) or Baseline (urine).
31. Female subjects who are breastfeeding or considering becoming pregnant during the study.
32. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

33. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.

34. History of clinically significant drug or alcohol abuse in the last 12 months.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

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

The history of previous use (including the duration of therapy, the highest known dose taken, reason for use and reason[s] for termination of treatment) of the immunomodulator, anti-TNF and/or biologic agents will be recorded in the appropriate eCRF. Subjects who have not been exposed to an anti-TNF will have their immunosuppressants recorded beyond the past 90 days.

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

5.2.3.2 Concomitant Therapy

Subjects who enter the study on aminosalicylates and/or MTX must remain on stable dose of this therapy for the entire study period.

Subjects who enter the study on Crohn's disease related antibiotics must remain on stable doses of this medication for at least 14 days prior to Baseline. Change in dose of Crohn's disease related antibiotics during the study will not be allowed for the 16-week induction

period, except in cases of treatment related toxicity or concerns about development of antibiotic resistance.

Subjects who enter the study on oral corticosteroids are not allowed to change the corticosteroid dose during the first 2 weeks of the treatment period. At Week 2, subjects who are taking corticosteroid therapy at Baseline must have their corticosteroid therapy tapered according to a tapering schedule specified below and in Section 5.3.1.1.

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

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

If a subject should experience an inadequate response during the corticosteroid taper, the subject may have their corticosteroid dose increased per the investigator's discretion up to and beyond the dose used at Baseline. Subjects in whom the maximum steroid dose exceeds the dose used at Baseline will be considered non-responders and will be censored for efficacy assessments from that point forward through the end of the study. These subjects will continue to be evaluated in the safety population.

Use of inhaled or topical dermatologic corticosteroids is not restricted.

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

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

The AbbVie Study Designated Physician identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following:
  - Etanercept (Enbrel®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Efalizumab (Raptiva®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Golimumab (Simponi®);
  - Vedolizumab (Entyvio®);
  - Infliximab (Remicade®);
  - Certolizumab pegol (Cimzia®).
- JAK inhibitors (e.g., tofacitinib [Xeljanz®])
- NSAIDs (except topical NSAIDs and the use of low dose aspirin for CV protection).
- Live vaccines are NOT allowed within 1 month prior to Screening and during the study. Examples of live vaccines include but are not limited to the following:
  - monovalent live attenuated influenza A (H1N1) (intranasal)
  - seasonal trivalent live attenuated influenza (intranasal)
  - herpes zoster, rotavirus
  - varicella (chicken pox)
  - measles-mumps-rubella (MMR) or measles mumps rubella varicella (MMRV)

  - oral polio vaccine (OPV)
  - smallpox
  - yellow fever
  - Bacille Calmette-Guérin (BCG)
  - typhoid
- 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 or during the Screening Period and during the study.
- Cyclosporine, tacrolimus, or mycophenolate mofetil use is prohibited within 30 days prior to Baseline and during the study.
- Azathioprine or 6-mercaptopurine (6-MP) use is prohibited within 10 days prior to Baseline and during the study.
- Investigational drugs of a chemical or biologic nature are prohibited within 30 days, or 5 half-lives (whichever is longer) of the drug prior to the Baseline and during the study.
- Use of strong CYP3A inhibitors (e.g., clarithromycin, conivaptan, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole, grapefruit juice) or strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) should be avoided from the Screening visit through the end of the study.

Note: Infliximab (Remicade®), Certolizumab (Cimzia®), Adalimumab (HUMIRA®), Vedolizumab (Entyvio®), Natalizumab (Tysabri®) are prohibited within 8 weeks prior to Baseline and during the study. Ustekinumab (Stelara®) is prohibited within 12 weeks prior to Baseline of during the study.

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

5.2.4 Contraceptive Recommendations

Contraception Recommendation for Females

A woman who is postmenopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Postmenopausal is defined as:

- Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 mIU/mL.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered a woman of childbearing potential and is required to practice at least one of the following highly effective method of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal ligation.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence

[e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the highly effective birth control methods listed above (excluding true abstinence).

It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy ABT-494. The concomitant methotrexate (MTX) that may have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant MTX and that duration of contraception after discontinuation of the MTX should be based on the local label.

Contraception Recommendation for Males

For a male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

A male subject who is sexually active with female partner(s) of childbearing potential, must agree from Study Day 1 through 30 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the contraceptive measures as defined in the protocol for female study subjects of childbearing potential.

  OR
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, male subject agrees not to donate sperm from Study Day 1 through 30 days after the last dose of study drug.

Male subjects are responsible for informing his partner(s) of the risk of becoming pregnant and reporting any pregnancy to the Investigator. If a pregnancy occurs, a partner authorization form requesting pregnancy outcome information will be requested from the pregnant partner.

It is important to note that contraception and sperm donation recommendations described above are specifically intended to prevent pregnancy during and after exposure to the investigational therapy ABT-494. The concomitant methotrexate (MTX) that may have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant MTX and that duration of contraception and the requirement not to donate sperm after discontinuation of the MTX should be based on the local label.

5.3 Efficacy and Safety Assessments/Variables

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 1. Study Activities

Activity	Screening[a]	Baseline (Week 0)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 28	Wk 36	Wk 44	Wk 52	Early Termination (ET) Visit	Unscheduled Visit	30-Day Follow-Up Visit
Informed Consent	X														
Inclusion/Exclusion[b]	X	X													
Medical/Surgical History[b]	X	X													
Prior and Concomitant Medications[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Endoscopy[d]	X					X	X					X	X		
Biopsy[e]	X					X	X					X	X		
SES-CD		X				X	X					X	X		
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[g]	X													X[v]	
Chest X-Ray[h]	X													X[v]	
PPD Skin Test or QuantiFERON TB Gold Test[i]	X														
Latent TB Risk Factor Questionnaire	X														
Blood Chemistry and Hematology	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Screening[a]	Baseline (Week 0)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 28	Wk 36	Wk 44	Wk 52	Early Termination (ET) Visit	Unscheduled Visit	30-Day Follow-Up Visit
Urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
hsCRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV and HCV Screening[l]	X														
ABT-494 Concentration[m]			X	X	X	X	X	X	X	X	X	X	X		
Pharmacodynamic biomarkers		X			X		X					X	X		
C. difficile toxin	X														
Stool Sample (fecal calprotectin)[n,o]	X			X			X		X			X	X		
Bristol Stool Chart	X			X			X		X			X	X		
Corticosteroid Taper[q]			X												
Crohn's Disease Activity Index (CDAI)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Inflammatory Bowel Disease Questionnaire (IBDQ)		X			X		X					X	X		

Table 1. Study Activities (Continued)

Activity	Screening[a]	Baseline (Week 0)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 28	Wk 36	Wk 44	Wk 52	Early Termination (ET) Visit	Unscheduled Visit	30-Day Follow-Up Visit
European Quality of Life 5 Dimensions (EQ-5D)		X			X		X					X	X		
Work Productivity and Impairment Questionnaire (WPAI)		X			X		X					X	X		
Abdominal Pain Rating Scale (0 – 10 Scale)		X				X	X								
Monitor Adverse Events[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing/ Administration		X	X	X	X	X	X	X	X	X	X				
Dispense Subject Diary	X														
Subject Diary Review		X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Activities (Continued)

Activity	Screening[a]	Baseline (Week 0)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 28	Wk 36	Wk 44	Wk 52	Early Termination (ET) Visit	Unscheduled Visit	30-Day Follow-Up Visit
Additional Samples Collection (Optional)															
Pharmacogenetic[s]		X													
Serologic markers[t]		X					X								
mRNA[t]		X					X								
Biopsy for gene expression[u]	X					X	X								

Wk = Week

a. The Screening period will be a minimum of 7 days but no more than 35 days. Baseline Visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits.

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

c. Physical examination performed at Screening, Baseline, Week 16 and Week 52/Early Termination Visits are full physical examinations which must include an assessment of extra-intestinal manifestations (EIMs) and a count of the number of cutaneous fistulas. Physical examinations and those performed at all other visits are symptom based but must include a count of the number of cutaneous fistulas.

d. Colonoscopy at/during the screening period or within 15 days of the Screening Visit will be used to calculate the SES-CD score at Baseline. Subject will be randomly assigned at Baseline to have endoscopy performed at Week 12 or Week 16.

e. Biopsy may be done when performing the endoscopy. Biopsy to confirm CD diagnosis may be done when performing the endoscopy if appropriate documentation for confirmation of the diagnosis does not exist. Biopsies to rule out dysplasia and colon cancer may be taken at the investigator's discretion.

f. Blood pressure, pulse rate, temperature, respiratory rate and weight should be performed before blood draws are performed. Height will be measured at Screening only (with shoes off and then adding 1 inch or 2.5 cm).

g. Subjects with normal ECG within 90 days of Screening would not require a repeat ECG, if documentation is available. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

Table 1. Study Activities (Continued)

h. Chest x-ray includes posterior-anterior (PA) and lateral views. Obtain chest x-ray for subjects with TB risk factors as identified by the TB risk factor questionnaire or for subjects living in areas endemic for TB or for subjects with positive PPD or QuantiFERON-TB Gold. Subjects can have a chest x-ray anytime during the study as warranted based on the opinion of the Investigator.

i. PPD skin test is to be read 48 to 72 hours after placement.

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.

k. Serum pregnancy test will be performed on all women of childbearing potential at Screening and at Week 52/ET. Urine pregnancy test will be performed locally at every visit for all women of childbearing potential. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

If required by country regulatory authorities, monthly pregnancy tests will be performed throughout the study.

l. Subjects will be tested for the presence of the hepatitis B Virus (HBV) and hepatitis C Virus (HCV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be exclusionary. For subjects who are negative for HBs Ag but are positive for core antibodies (HBc Ab), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

m. For all subjects, a PK sample will be collected at Week 2, within 1 to 3 hours after dosing, if possible. At Week 4, Week 8, Week 12, Week 16, Week 20, Week 28, Week 36, Week 44 and Week 52/ET, a blood sample for PK will be collected at any time during the visit, and preferably within 1 to 8 hours after the last dose. Patients can take the dose on visit days at their regular schedule and not necessarily at the clinic. The date and accurate time of the PK sample collection and the last ABT-494 dose will be recorded in the CRF to the nearest minute.

n. Stool sample will be collected at each time point indicated. For the visit that endoscopy will be conducted, stool sample should be collected prior to endoscopy.

o. A stool sample will be collected for fecal calprotectin analysis at each time point indicated. Subjects will be asked to provide a stool sample at the visit, if possible, or subjects will be sent home with instructions and stool sample supplies (supplies will be provided).

p. Subject is mandated to begin corticosteroid taper at Week 2.

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

r. Only if subject provides written consent to collect the pharmacogenetic sample; if the informed consent form is not signed, no pharmacogenetic sample can be collected. The sample is preferred to be collected at BL.

Table 1. Study Activities (Continued)

s. Only if subject provides written consent to collect the serum biomarkers and mRNA samples; if the informed consent form is not signed, no serum biomarkers and mRNA can be collected.

t. Only if subject provides written consent to collect biopsy samples for gene expression analysis; if the informed consent form is not signed, no biopsy for gene expression can be collected. Biopsies will be obtained at baseline and as the Week 12/16 endoscopy, based on the colonoscopy assignment for Week 12 or 16.

u. Optional tests, only if determined by the investigator and based on the medical assessment.

v. Laboratory tests performed during the Screening period can be repeated in case the abnormalities are considered to be transient by the investigator.

5.3.1.1 Study Procedures

The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of drug concentration measurements (discussed in Section 5.3.2), pharmacogenetic and pharmacodynamic biomarkers, serologic markers, mRNA and gene expression samples (discussed in Section 5.3.1.2, Section 5.3.1.3, Section 5.3.1.4, Section 5.3.1.5, and Section 5.3.1.6, respectively), 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. A separate informed consent will be required for each subject in order to participate in the optional pharmacogenetic analysis, serological biomarker, mRNA analysis and gene expression. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

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

Medical and Surgical History

A complete medical and surgical history, including CD-onset date, history of CD medication use, and history of alcohol and tobacco use will be obtained from each subject at the Screening Visit. An updated medical history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment, and updated as necessary.

Prior corticosteroid, azathioprine, 6-MP, MTX and aminosalicylate use will be asked. If subjects have/had ever been treated with these medications, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will be recorded in subjects' source document and in appropriated eCRF. The details of dates of administration and dosages will be also recorded within the past 90 days.

A detailed anti-TNF therapy history will be recorded, this includes names of anti-TNF used, duration of therapy, doses, reason (s) for use and reason(s) for termination of treatment with these products (e.g., Inadequate Response, Intolerance, primary failure, secondary failure) must be documented in the subjects' source documents and in appropriated eCRF.

A detailed medical history with respect to Inadequate Response and/or Intolerance to an immunomodulator or anti-TNF agent must be documented in the subjects source documents. A detailed medical history with respect to TB exposure will be documented. This information will include BCG vaccination, cohabitation with individuals who have had TB, and residence or work in TB endemic locations.

Physical Examination

A physical examination including evaluation of extra intestinal manifestations will be performed at the designated study visits as specified in Table 1.

A full physical examination will be performed at Screening, Baseline, Week 16 and Week 52/ET Visit and must include an assessment of extra-intestinal manifestations (EIMs) and a count of the number of cutaneous fistulas. Symptom-based physical examinations will be performed at all other visits must include a count of the number of cutaneous fistulas.

The physical examination at the Baseline Visit will serve as the Baseline physical examination for the entire study. A count of the number of cutaneous fistulas draining upon gentle compression must be performed during each physical exam. Fistulas will be classified as abdominal or perianal/anal. Physical examination abnormalities noted by the

Investigator at Baseline prior to the first dose of study drug (including fistulas and fissures) will be recorded in the subject's medical history. Abnormalities noted after the Baseline Visit and first dose of study drug will be evaluated and documented by the Investigator as to whether or not these are adverse events. All findings whether related to an adverse event or part of each subject's medical history will be captured on the appropriate eCRF page.

A symptom-directed physical examination will be performed when necessary.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, body weight, and body temperature will be obtained at each visit. Blood pressure, pulse rate and respiratory rate should be performed before blood draws are performed. Height will be measured at the Screening Visit only (with shoes off). All measurements will be recorded in metric units where applicable.

Chest X-Ray (CXR)

A chest x-ray (posterior-anterior and lateral views) will be obtained for all subjects with TB risk factors as identified by the TB risk factor questionnaire (Appendix G) or for subjects living in areas endemic for TB or for subjects with a positive PPD or QuantiFERON-TB Gold. The Investigator may obtain a Baseline chest x-ray if clinically indicated for a specific subject. Subjects can have a chest x-ray anytime during the study as warranted based on the opinion of the Investigator.

The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report.

Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at the designated study visits as specified in Table 1. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. Any clinically significant findings will be documented

in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible 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.

TB Screening

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a subject has active or latent tuberculosis.

For all subjects, evidence of increased risk for TB will be assessed by a questionnaire (Appendix G) and testing (PPD skin test or QuantiFERON-TB Gold [or equivalent]). Subjects with a negative QuantiFERON®-TB Gold test OR negative PPD TB skin test AND no evidence of increased TB risk based on the questionnaire may be enrolled. Subjects with a positive QuantiFERON-TB Gold test OR a positive PPD skin test (defined as 5 mm of induration or greater) OR at increased risk of TB based on questionnaire/geography should have a chest x-ray. Subjects with evidence of latent TB may be enrolled after at least 2 weeks of prophylactic treatment per local guidelines.

If a subject had a negative PPD test or QuantiFERON-TB Gold test (or interferon-gamma release assay-IGRA-equivalent such as T-SPOT TB test) test within 90 days prior to Screening and all protocol required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases must be discussed with the AbbVie Study Designated Physician.

Subjects should be screened for TB using either PPD or IGRA. In the event both a PPD test and an IGRA test are performed, if either one is positive the subject will be considered to be positive. If the IGRA test is indeterminate, the site should repeat the test. If the second IGRA test is also indeterminate, the subject is considered to be positive.

Subjects with evidence of latent TB may be enrolled after at least 2 weeks of prophylactic treatment per local guidelines.

Subjects with evidence of active TB infection are excluded.

The results of the TB test(s) will be retained at the site as the original source documentation.

QuantiFERON-TB Gold Test (or IGRA Equivalent such as T-SPOT TB Test)

QuantiFERON-TB Gold test (or IGRA equivalent such as T-SPOT TB test) will be performed at Screening. The analyses will be performed by a certified laboratory.

OR

TB Skin Test

A PPD skin test (alternatively, also known as a TB Skin Test or Mantoux test) will be performed at Screening according to standard clinical practice. The TB Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration equal to or greater than 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."

Pregnancy Tests

A serum pregnancy test will be performed at the Screening and Week 52/ET Visit on all female subjects of childbearing potential.

Women of childbearing potential includes all women who are not surgically sterile (both ovaries removed or uterus removed) or post-menopausal (defined as no menses for at least one year, without an alternate reason for amenorrhea).

At the Baseline Visit, subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. If the serum pregnancy test is positive, dosing must be stopped and the subject must be discontinued from the study.

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

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

Hepatitis B and C Testing

All subjects will be tested for the presence of the hepatitis B Virus (HBV) and hepatitis C Virus (HCV) at Screening. Subjects with hepatitis B (HBs Ag positive [+] or detected sensitivity on the HBV DNA PCR qualitative test for core antibodies (HBc Ab) positive subjects) or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be excluded. Subjects who have been vaccinated against hepatitis B and are HBs Ab positive may be enrolled.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 2. Blood draws should be performed after all clinical assessments and questionnaires (IBDQ, etc.) and vital sign determinations are obtained during a visit.

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

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

The blood samples for serum chemistry tests should be collected following a minimum 8-hour fast, when possible. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation. The fasting status will be recorded in the laboratory request, source document and CRF.

Table 2. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**[a]
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Reticulocyte count	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Creatine Phosphokinase (CPK) Sodium Potassium Chloride Bicarbonate Calcium Inorganic phosphorus Uric acid Cholesterol LDL cholesterol HDL cholesterol Total protein Glucose Triglycerides Chloride	Specific gravity Ketones pH Protein Glucose Blood Nitrite Leukocytes Microscopic Examination
	Stool Samples Collected	**Other Laboratory Tests**
	C. difficile toxin Fecal calprotectin	Serum pregnancy test Urine pregnancy test High sensitivity C-reactive protein (hs-CRP) Hbs Ag HBs Ab HBc Ab HBV DNA PCR reflex only HCV Ab HCV RNA reflex only PPD QuantiFERON-TB Gold Pharmacodynamic biomarkers Pharmacokinetic
Additional Samples Collected (Optional)		
Pharmacogenetic mRNA Serologic markers Biopsy for gene expression		

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

Urinalysis

Urine samples will be obtained and sent to the central laboratory for the tests listed in Table 2. Microscopic urinalysis will only be performed by the central laboratory if the

dipstick UA results are abnormal, where abnormal is defined as leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace.

Other Laboratory Assessments

hs-CRP

Blood samples for high-sensitivity C-reactive protein (hs-CRP) will be obtained. Blood draws should be performed after all clinical assessments, questionnaires (IBDQ, etc.), and vital sign determinations are obtained. The hs-CRP results from Week 2 through Week 16 will be blinded to sites/sponsor. The hs-CRP results after Week 16 will be un-blinded.

hs-CRP will be performed by Central Lab. However, for the purpose of evaluating Inadequate Response criteria, hs-CRP can also be done at local lab. At Week 20, since the Week 16 hs-CRP will still be blinded, the hs-CRP performed by the local lab or the Week 20 Central Lab result will be used for the assessment of Inadequate Response.

Stool Samples Collected

Fecal Calprotectin

Fecal calprotectin will be performed for all subjects as indicated in Table 1. Subjects will be asked to provide a stool sample, subjects will be sent home with instructions and a stool sample supplies (supplies will be provided).

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

All stool samples should be collected before any bowel preparation for endoscopy is started. The central laboratory will be utilized to process and provide results for these laboratory tests.

The stool sample collected during the Screening Period will be used for the Baseline assessment (prior to receiving study drug).

C. Difficile

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

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

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

CDAI

A CDAI will be calculated from a subject diary, physical exam, and appropriate laboratory values at all study visits beginning at Screening. The Screening Period will be a minimum of 7 days but will not exceed 35 days. The CDAI calculated during Screening will serve as the Baseline CDAI.

For calculation of CDAI scores, beginning with the Week 2 through Week 52, the CDAI scores must be calculated using a hematocrit value from the preceding visit laboratory work.

CDAI at Visit	Hematocrit Value Utilized
Week 2	Baseline
Week 4	Week 2
Week 8	Week 4
Week 12	Week 8
Week 16	Week 12
Week 20	Week 16
Week 28	Week 20
Week 36	Week 28
Week 44	Week 36
Week 52	Week 44

For calculating CDAI, to answer questions one (1) through three (3), entries from the 7 days prior to the day of study visit should be used as recorded by the subject from the diary.

Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit.

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

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

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

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

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

If the body weight obtained at the time of assessment is not captured in kilograms (kg), then when converting into kgs, rounding should occur using the second digit after the decimal (also known as the hundredth place) where if the number is 0 – 4 then keep the first digit after the decimal (also known as the tenth place) unchanged. If the second digit after the decimal is 5 – 9 then round up the first digit after the decimal (e.g., 90.246 would be captured as 90.2, 97.687 would be captured as 97.7).

The subtotal of box 8 should not be rounded to a whole number. The calculation of the CDAI score is in Appendix D.

Outcomes and Questionnaires

- IBDQ – Inflammatory Bowel Disease Questionnaire (IBDQ) will be completed at the time points indicated in Table 1.
- WPAI – Work Productivity and Activity Impairment Questionnaire (WPAI) will be completed at the time points indicated in Table 1. The data in the subject completed questionnaire will be transferred to the appropriate eCRF (Electronic Case Report Form) by the site personnel at each study visit (Appendix C).
- EQ-5D – European Quality of Life 5 Dimensions, a standardized questionnaire for use as a measure of health outcome will be completed at the time points indicated in Table 1.
- Abdominal Pain Rating Scale (0 – 10 Scale) (Appendix I).

Corticosteroid Taper

At Week 2, subjects who are on prednisone or budesonide must have their corticosteroid dose tapered according to the following proposed schedule or based on Investigators' discretion:

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

If a subject should experience an inadequate response during the corticosteroid taper, the subject may have their corticosteroid dose increased, per the investigator's discretion, up to and beyond the dose used at Baseline. Subjects in whom the maximum steroid dose exceeds the dose used at Baseline will be considered non-responders and will be censored for efficacy assessments from that point forward through the end of the study. These subjects will continue to be evaluated in the safety population.

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/ET 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 dispensed to subjects beginning at Baseline and at all study visits through Week 52. No study medication will be dispensed at Week 52.

(Refer to Section 5.5 for additional information.)

Endoscopy

An endoscopy will be performed on the following visits:

- During Screening*
- Week 12 or Week 16
- Week 52/Early Termination

For those subjects who discontinue the study between Weeks 8 and 12 the endoscopy performed at the Early Termination Visit will be used as the Week 12 endoscopy result. An endoscopy will not be performed if a subject discontinues the study prior to Week 8.

In addition, for those subjects who discontinue the study during the extension phase, an endoscopy will not be performed if a subject discontinues the study prior to Week 28.

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

1. biopsy confirmation of the diagnosis is available according to section "Biopsy During Endoscopy" below.
2. the endoscopy took place within 15 days of Screening Visit.
3. the endoscopy was recorded in a video format as the endoscopic eligibility will be determined by the central reviewers. The same endoscopist, where possible, should perform all endoscopies.

An ileo-colonoscopy will be performed and recorded at the site in a video format and will be reviewed by a central reviewer who is blinded to the therapy, during the Screening Period (or within 15 days of the Screening Visit), Week 12 or Week 16 and the Week 52/ET Visit. There will be a window of ± 7 days to conduct the ileocolonoscopy. This window may be extended as necessary after consultation with the AbbVie Study Designated Physician in case of external, not subject-related circumstances

(e.g., scheduling conflict). The central reviewer will evaluate the data and provide the endoscopy subscore for calculating the Simplified Endoscopic Score (SES CD). Discrepancies between the central reviewer and the site endoscopist regarding a subject's score will be finally judged through adjudication by a second central reviewer. The adjudicator will not provide an assessment but will select the assessment with whom he/she agrees. The adjudicator's assessment will be considered final. Endoscopic eligibility will be determined by the central reviewers. If, in the opinion of the Investigator, the Screening endoscopy does not indicate the SES-CD criteria confirming study eligibility, the subject should be screen-failed and the video should not be sent for central review.

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

The endoscopy during the Screening Period (or endoscopy performed within 15 days of the Screening Visit), Week 12 or Week 16 and Week 52/ET will be used to provide the endoscopy subscores for calculating the Simplified Endoscopic Score (SES CD) at Screening, Week 12 or Week 16 and Week 52/ET, respectively, refer to Appendix F.

The endoscopy subscores by segment will be noted in the subject's source documents and in the database but the central reviewer's endoscopy subscore will be used for the efficacy analyses.

For stratification at Week 16 re-randomization, the local reading (at Week 12 or Week 16) will be compared with the baseline central reading in order to determine response status.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available a diagnostic biopsy from the most affected area of the 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 per the Investigator's discretion during any endoscopy performed during this study and evaluated by the local pathologist.

If any biopsy sample(s) are obtained, it should also be recorded on the video.

Any biopsy sample(s) will be collected from the respective bowel segment during the withdrawal of the endoscope and after sufficient recording for the central reader to calculate the SES-CD.

The signed pathology report will be monitored by the responsible Clinical Research Associate (CRA) and kept with the subject's source documents onsite. Subjects should not be enrolled if colon dysplasia or colon cancer is discovered at Screening endoscopy or endoscopy performed within 15 days of the Screening Visit.

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.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

An optional whole blood sample for DNA isolation will be collected on Baseline Visit from each subject who consents to provide samples for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

The sample collection tubes will minimally be labeled with "PG-DNA," protocol number, subject number and the study day. Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of pharmacogenetic samples will be provided outside of this protocol.

Abbvie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-494 (or drugs of this class) continues but no longer than 20 years after study completion (where allowed by local guidelines).

5.3.1.3 Collection and Handling of In Vivo Pharmacodynamic Biomarker Variables

Serum samples will be collected at time points specified in Table 1 to assess JAK activity effects on certain lymphocyte subsets including T (CD4+ and CD8+), B, NK cell subsets, reticulocyte and other cell types.

Instructions on preparation and shipment of pharmacodynamic (in vivo biomarkers) samples will be provided by a certified laboratory or the sponsor outside this protocol. In vivo biomarkers will be assayed using a validated method under the supervision of the Bioanalysis Department at AbbVie.

5.3.1.4 Collection of Samples for Serologic Markers

Optional blood samples for serologic markers analysis will be collected at from each subject who consents to provide samples the time points indicated in Table 1. Please refer to the laboratory manual for specific instructions.

The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

The frozen 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 samples to AbbVie or the designated laboratory for serologic markers analysis and long-term storage as allowed by regional/local law and as defined in the approved informed consent form.

5.3.1.5 Collection of Samples for mRNA Assays

Optional whole blood samples for mRNA will be collected from each subject who consents to provide samples at the time points indicated in Table 1. Please refer to the laboratory manual for specific instructions.

The frozen samples for mRNA analysis will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. An inventory of the samples included will accompany the package. Arrangements will be made with the central laboratory for the shipment of samples to AbbVie or the designated laboratory for mRNA analysis and long-term storage as allowed by regional/local law and as defined in the approved informed consent form.

5.3.1.6 Collection of Samples for Gene Expression

Optional gene expression samples may be evaluated in approximately 80 subjects. A separate informed consent will be required for participation in this part of the protocol. Endoscopic biopsy samples for gene expression analysis will be obtained from segments of the colon and the ileum with the most significant abnormalities at the time of screening endoscopy. Three biopsy samples each should be obtained from both the colon and ileum. In patients with isolated active ileal disease, collect 3 biopsy samples from the ileum only. The location biopsied at screening endoscopy should be recorded, and Week 12/16 biopsies should be obtained from the same segment. Care should be taken to avoid the bed of ulcers, instead samples should be obtained from the area surrounding ulcers when these exist. Sample handling instructions will be provided in the laboratory manual for gene expression analysis and long-term storage as allowed by regional/local law and as defined in the approved informed consent form.

5.3.2 Drug Concentration Measurements

Blood samples for assay of ABT-494 will be collected as follows:

- At Week 2 visit, a PK sample will be collected within 1 to 3 hours after dosing if possible.
- At Week 4, Week 8, Week 12, Week 16, Week 20, Week 28, Week 36, Week 44 and Week 52/ET, a blood sample for PK will be collected at any time during the visit, and preferably within 1 to 8 hours after the last dose.

Patients can take the dose on visit days at their regular schedule and not necessarily at the clinic. The accurate time of the PK sample collection and last ABT-494 dose will be recorded on the CRF to the nearest minute.

5.3.2.1 Handling/Processing of Samples

Detailed instructions for the handling and processing of samples will be provided by central laboratory. The plasma samples will be shipped to Central Laboratory. ABT-494 plasma concentration will be determined at AbbVie.

5.3.2.2 Disposition of Samples

The frozen plasma samples for ABT-494 assays will be packed in dry ice sufficient to last during transportation and shipped from the study site to the Central Laboratory according to instructions in the central laboratory Lab Manual. An inventory of the samples included will accompany the package.

5.3.2.3 Measurement Methods

Plasma concentrations of ABT-494 will be determined under the supervision of the Drug Analysis Department at AbbVie using validated liquid chromatography/mass spectrometry methods.

5.3.3 Efficacy Variables

The following endpoint definitions apply to the efficacy variables described below:

- **Remission:** Endoscopic remission AND Clinical remission
- **Response:** Endoscopic response AND Clinical response
- **Endoscopic remission:** SES-CD ≤ 4 and at least two point reduction versus Baseline and no subscore > 1 in any individual variable
- **Endoscopic response:** SES-CD at least 25% reduction from Baseline
- **Clinical remission:** average daily stool frequency ≤ 1.5 and not worse than Baseline AND average daily abdominal pain ≤ 1.0 and not worse than Baseline
- **Clinical response:** average daily stool frequency at least 30% reduction from Baseline and average daily abdominal pain not worse than Baseline OR average daily abdominal pain at least 30% reduction from Baseline and average daily stool frequency not worse than Baseline

5.3.3.1 Primary Variables

The co-primary endpoints of this study are:

1. Proportion of subjects who achieve endoscopic remission at Week 12/16.
2. Proportion of subjects who achieve clinical remission at Week 16.

5.3.3.2 Secondary Variables

The secondary endpoints *(Double-Blind Induction Treatment Period)* include:

- Proportion of subjects who achieve CDAI < 150 at Week 16.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline at Week 16.
- Proportion of subjects who achieve clinical remission at Week 12.
- Proportion of subjects who achieve remission at Week 16 (endoscopic remission at Week 12/16 and clinical remission at Week 16).

- Proportion of subjects who achieve response at Week 16 (endoscopic response at Week 12/16 and clinical response at Week 16).
- Proportion of subjects with endoscopic response at Week 12/16.
- Proportion of subjects who achieve clinical response at Week 16.
- Proportion of subjects with an average daily SF $\geq$ 2.5 AND average daily AP $\geq$ 2.0 at Baseline who achieve clinical remission at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve CDAI < 150 at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 12/16 and clinical remission at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission at Week 16.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 12/16.
- Change from Baseline in fecal calprotectin level at Week 16.
- Change from Baseline in hs-CRP at Week 16.
- Change in IBDQ from Baseline at Week 16.
- Proportion of subjects with isolated ileal Crohn's disease who achieve remission at Week 16.

The secondary endpoints (Double-Blind Extension Phase) include:

- Proportion of subject who achieve remission at Week 52.
- Proportion of subjects who achieve endoscopic remission at Week 52.
- Proportion of subjects who achieve clinical remission at Week 52.
- Proportion of subject who achieve response at Week 52.
- Proportion of subjects who achieve endoscopic response at Week 52.
- Proportion of subjects who achieve clinical response at Week 52.
- Proportion of subjects with an average daily SF $\geq$ 2.5 AND average daily AP $\geq$ 2.0 at Baseline who achieve clinical remission at Week 52.

- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieved CDAI < 150 at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve remission at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission at Week 52.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission at Week 52.
- Proportion of subjects who achieve CDAI < 150 at Week 52.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline at Week 52.
- Change from Baseline in fecal calprotectin level at Week 52.
- Change from Baseline in hs-CRP at Week 52.
- Change in IBDQ from Baseline at Week 52.
- Change in EIMs from baseline at Week 52.
- Proportion of subjects with isolated ileal Crohn's disease who achieve remission at Week 52.

5.3.3.3 Additional Efficacy Variables

The additional endpoints include:

- Proportion of subject who achieve remission over time.
- Proportion of subjects who achieve endoscopic remission over time.
- Proportion of subjects who achieve clinical remission over time.
- Proportion of subject who achieve response over time.
- Proportion of subjects with endoscopic response over time.
- Proportion of subjects who achieve clinical response over time.
- Proportion of subjects who achieve CDAI < 150 over time.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline over time.

- Change in WPAI from Baseline over time.
- Change in EQ5D from Baseline over time.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve CDAI < 150 over time.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve remission over time.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve clinical remission over time.
- Proportion of subjects taking corticosteroids at Baseline who discontinued corticosteroid use and achieve endoscopic remission over time.
- Change from Baseline in fecal calprotectin level over time.
- Change from Baseline in hs-CRP over time.
- Change in IBDQ from Baseline over time.
- SES-CD endpoints with adjustment for segments visualized.
- The proportion of subjects in each treatment group with no draining fistulas at Week 16 among subjects with draining fistula at Baseline.
- The proportion of subjects in each treatment group with ≥ 50% reduction from Baseline in the number of draining fistulas at Week 16 among subjects with draining fistula at Baseline.
- The proportion of subjects in each treatment group with no draining fistulas at Week 52 among subjects with draining fistula at Baseline.
- The proportion of subjects in each treatment group with ≥ 50% reduction from Baseline in the number of draining fistulas at Week 52 among subjects with draining fistula at Baseline.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Plasma ABT-494 concentrations will be obtained at the times indicated in Table 1. A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of ABT-494 oral clearance (CL/F) and volume of distribution (V_{ss}/F). Additional parameters may be estimated if useful in the interpretation of the data.

5.3.6 Pharmacogenetic and Serologic Variables

5.3.6.1 Pharmacogenetic Variables

For patients who consent to this optional testing, DNA samples may be analyzed for genetic factors contributing to the disease or to the subject's response to ABT-494, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ABT-494 or drugs of this class. The samples may also be used for the development of diagnostic tests related to ABT-494 (or drugs of this class) or the disease. The results of pharmacogenetic analyses may 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 guidelines, the samples will be retained for up to 20 years after completion of the study research. A separate informed consent will be required for participation in this part of the protocol.

5.3.6.2 Serologic Marker and mRNA Variables

For patients who consent to this optional testing, serum and mRNA samples will be collected and stored for possible future exploratory analyses of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or

development of adverse events. For example, samples may be analyzed for plasma and serum proteins, peptides, and non-protein soluble factors such as lipids that may help predict disease behavior and help determine more severe disease phenotypes and response to JAK inhibitors. These samples may also be used for the development of diagnostic tests. Results of these types of exploratory analyses, if any, will not be reported with the study summary.

To protect subjects' confidentiality, the samples will be coded with the subjects' study identifiers. The key between the subjects' study identifiers and the subjects' personal identifiers will be held at the investigator site and will not be accessible to AbbVie researchers. Unless a certain time limit is required by a site's local regulations, samples will be stored for up to 20 years in AbbVie's Immunology Biobank or a laboratory designated by AbbVie, which is a secure facility. Abbvie will be responsible for the long term storage and destruction of the samples.

A separate informed consent will be required for participation in this part of the protocol. The samples will only be used for the purposes described here and in the informed consent. Any other uses would require additional ethical approval.

5.3.6.3 Gene Expression Variables

For patients who consent to this optional testing, gene expression may be evaluated in approximately 80 subjects. A separate informed consent will be required for participation in this part of the protocol.

Biopsy will be collected and stored for possible future exploratory analyses of gene expression. Results of these types of exploratory analyses, if any, will not be reported with the study summary.

To protect subjects' confidentiality, the samples will be coded with the subjects' study identifiers. The key between the subjects' study identifiers and the subjects' personal identifiers will be held at the investigator site and will not be accessible to AbbVie researchers. Unless a certain time limit is required by a site's local regulations, samples

will be stored for up to 20 years in AbbVie's Immunology Biobank or a laboratory designated by AbbVie, which is a secure facility. AbbVie will be responsible for the long term storage and destruction of the samples.

The samples will only be used for the purposes described here and in the informed consent. Any other uses would require additional ethical approval.

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 of the following occur:

- Clinically significant abnormal laboratory results or adverse events, which rule out continuation of the study medication, as determined by the Investigator and the AbbVie SDP.
- Serious infections (e.g., sepsis) which would put the subject at risk for continued participation in the trial 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.
- 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 (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study medication.

- Subject has known high grade dysplasia of the gastrointestinal tract or 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 significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial 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 Week 52/ET 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 visit will occur for all subjects, approximately 30 days after the last dose of study medication to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last study drug dose and the primary reason for early termination. 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 and documented in the subject's source documentation.

Subjects who discontinue the study prematurely will not be replaced.

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

Study drug will be taken orally twice a day for 52 weeks beginning on Baseline. Subjects will be instructed to take two daily doses of 2 capsules (four capsules daily) as described in the tables below at approximately the same time each day.

At or after Week 20, if subject met the criteria of inadequate response, subject may be eligible to receive the Open-Label ABT-494 12 mg BID and would take 2 capsules daily.

If subject continues to meet the criteria of inadequate response, subject could move to receive the Open-Label ABT-494 24 mg BID (4 capsules daily). The study drug can be taken with or without food.

5.5.1 Treatments Administered

During the Double-Blind Induction Period (Weeks 1 – 16)

Treatment Group	ABT-494 3 mg	ABT-494 12 mg	Placebo for ABT-494 3 mg or 12 mg
ABT-494 3 mg BID	1	0	1
ABT-494 6 mg BID	2	0	0
ABT-494 12 mg BID	0	1	1
ABT-494 24 mg BID	0	2	0
ABT-494 24 mg QD (AM)	0	2	0
ABT-494 24 mg QD (PM)	0	0	2
Placebo	0	0	2

During the Double-Blind Extension Phase (Weeks 16 – 52)

Treatment Group	ABT-494 3 mg	ABT-494 12 mg	Placebo for ABT-494 3 mg or 12 mg
ABT-494 3 mg BID	1	0	1
ABT-494 6 mg BID	2	0	0
ABT-494 12 mg BID	0	1	1
ABT-494 24 mg QD (AM)	0	2	0
ABT-494 24 mg QD (PM)	0	0	2

Study Drug for Administration During the Open-Label due to the Inadequate Response

Treatment Group	ABT-494 12 mg
ABT-494 24 mg BID	2
ABT-494 12 mg BID	1

5.5.2 Identity of Investigational Product

Investigational Product	ABT-494		Placebo for 3 mg or 12 mg
Mode of Administration	Oral	Oral	Oral
Dosage Form	Capsule	Capsule	Capsule
Strength (mg)	3	12	0

5.5.2.1 Packaging and Labeling

AbbVie will supply blinded study medication in weekly kits. Each Kit will contain a blister card for 1 week of study medication plus 3 extra daily doses. Daily doses are identified on each blister card as Day 1 through Day 7, respectively. Additional study drug is identified on each blister card as "Extra." Open-label study medication will be supplied in bottles.

Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements.

Labels must remain affixed to the blister cards, and bottles and must not be concealed by any over-labeling. All blank spaces on the label will be completed by site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug

The study drug must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The controlled storage area should have a temperature recording device. A storage temperature log is to be maintained to document proper storage conditions. Malfunctions or any temperature excursions must be reported to the sponsor immediately. In case of a temperature excursion, study medication should be quarantined and not dispensed until AbbVie deems the medication acceptable. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on

site according to local procedures or regulations or returned to the destruction depot by the site monitor.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, the telephone number and call-in directions for the IRT will be provided to each site.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. Subjects who meet the inclusion and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized 1:1:1:1:1:1 to one of six treatment groups at Baseline (Week 0) in a double-blind manner. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the Statistics Department at AbbVie.

IRT will provide the appropriate medication kit number(s) to dispense to each subject. Study drug will be administered at the study visits as summarized in Section 5.5. Returned study medication should not be re-dispensed to any subject.

At Week 16, all subjects will be re-randomized in a ratio of 1:1:1 to the three double-blind doses of ABT-494 (3 mg BID, 6 mg BID or 12 mg BID). The subjects who were re-randomized at Week 16 to ABT-494 24 mg QD prior to Protocol Amendment 2 will continue to receive the same double-blind dose until Week 52/PD.

The re-randomization will be stratified by the induction dose received during the first 16 weeks and by response status (responder versus non-responder) at Week 16. All subjects will keep the same unique subject identification number throughout the study.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects will be randomly assigned to one of the six treatment groups (ABT-494 3 mg BID, ABT-494 6 mg BID, ABT-494 12 mg BID, ABT-494 24 mg BID, ABT-494 24 mg QD, placebo) at Baseline by the IRT system as described in Section 5.5.3.

Subjects should take study medication as outlined in Section 5.5.1.

Each subject's dosing schedule should be closely monitored by the site at each study visit by careful review of the subject's dosing diary. This will ensure that all subjects enrolled into the study maintain their original dosing schedule beginning with the first dose of study drug (Baseline/Week 0).

If a subject should forget to take their study drug dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 6 hours before their next scheduled dose. If a subject only remembers the missed dose within 6 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time. If the subject experiences a study drug interruption > 10 days, they should notify their study site physician, and the Investigator should consult with the study designated physician about discontinuing the subject from the study.

5.5.5 Blinding

The Investigator, study site personnel, the subject and all AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment throughout the course of the study. The IRT will provide access to blinded subject treatment information in the case of a medical emergency. In the event of medical situation that requires unblinding of the study drug assignment the Investigator is requested to contact the AbbVie Study Designated Physician (SDP) prior to breaking the blind, as long as this communication does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting AbbVie

SDP, the Investigator can directly access the IRT system to break the blind without AbbVie agreement. In the event that the blind is broken before notification to AbbVie SDP, it is requested that the AbbVie SDP be notified within 24 hours of the blind being broken. Also, the date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Throughout the duration of the double-blind periods of the study, the Investigator, site personnel, and subjects will remain blinded to the subject's treatment group. AbbVie will remain blinded to the induction and extension periods data until those data are locked and analyzed as part of the first and potentially second interim analysis, respectively.

5.5.5.1 Blinding of Investigational Product

In order to maintain the blind, the ABT-494 capsules and Placebo capsules provided for the study will be identical in appearance.

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

Data will be unblinded for review by the Independent Data Monitoring Committee (IDMC) by an unblinded statistician not involved in the planning, execution or analysis of the study. The process for unblinding study data and ensuring its confidentiality will be described in the Independent Data Monitoring Committee Charter for this study. The IDMC will advise the sponsor as to study continuation and/or modification.

5.5.6 Treatment Compliance

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

Subject dosing will be recorded on a subject dosing diary. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. The study site personnel will document compliance in the study source documents.

5.5.7 Drug Accountability

In addition, an IRT will be used to document investigational product accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number and the identification of person dispensing the drug.

All empty study drug blister cards will be inventoried by the site and verified by the site monitor. Empty study drug blister cards should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty blister cards will be retained until the site monitor is on site to confirm the returned medication. Site monitor(s) and site staff will complete study medication accountability via IRT source documents, subject dosing diaries, and by visually inspecting the blister cards whenever possible. After drug accountability has been completed, unused medication will be destroyed on site according to local procedures or regulations or returned to the destruction depot by the site monitor. A copy of the destruction methodology should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

ABT-494 is a potent JAK1 selective inhibition that has been associated with endoscopic improvement and healing of the intestinal mucosa in preclinical animal models. More recently, filgotinib, a JAK1 inhibitor in Phase 2 clinical development in Crohn's disease was associated with superior clinical remission versus placebo.[33] This study included subjects who could have been inadequate responders or intolerant to either immunomodulators or anti-TNF therapies. Of note, this treatment effect was more prominent in subjects who have inadequate responders to immunomodulators only. AbbVie proposes to include this patient population to assess the effect of ABT-494 and whether they would benefit the most from such therapy.

The proposed study is a 52-week, randomized, double-blind, placebo-controlled study to compare multiple doses of ABT-494 versus placebo in moderately to severely active CD patients with failure or intolerance to immunomodulators or anti-TNF biologic therapy. In order to assess the potential of ABT-494 to benefit patients with CD, we will enroll

patients with active disease (confirmed by central reading of endoscopy video) and assess the potential of ABT-494 to induce clinical remission and endoscopic improvement. The 16-week induction therapy period is generally accepted as the timeframe during which an effective treatment would be expected to produce clinical benefit in CD.

During the double-blind extension phase of this study, all patients will have an opportunity to be treated with ABT-494 in order to assess the potential of ABT-494 to maintain clinical remission in patients who have responded to treatment with ABT-494.

5.6.1 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CD. All clinical and laboratory procedures in this study are standard and generally accepted. Central reading of endoscopy films will increase study rigor and ensure enrollment of patients with active inflammation.

5.6.2 Suitability of Subject Population

Adult male and female subjects with active CD who meet all inclusion criteria and none of the exclusion criteria are eligible for this study. The specific subject population chosen was based on the unmet medical need for subjects with evidence of mucosal inflammation and who have had an inadequate response or intolerance to immunomodulators or anti-TNF biologic therapy.

5.6.3 Selection of Doses in the Study

This study is designed to evaluate the efficacy and safety/tolerability of ABT-494 in subjects with CD and to define the dose response profile of this compound. The dose selection for ABT-494 in the present study was based on the preliminary analysis of PK, PD, safety and tolerability data from the single ascending dose study of ABT-494 in healthy subjects (single doses ranging from 1 to 48 mg), the multiple ascending dose study of ABT-494 in healthy subjects (multiple doses ranging from 3 to 24 mg BID for 14 days), as well as the multiple dose study of tofacitinib 5 mg BID for 14 days in healthy

subjects. Based on ex-vivo experiments conducted during the Phase 1 studies, we know that doses selected for this study significantly inhibit IL-6 signaling via the JAK1 pathway. In addition, the dose range selected has been shown to be well tolerated in healthy volunteers and includes exposure anticipated to result in JAK1 selective exposure that may produce both efficacy and favorable benefit:risk profile. Study drug will be dosed for 52 weeks and will not exceed 24 mg BID.

During the extension Phase, the ability of ABT-494 to maintain patients in remission will be assessed, with opportunity for dose escalation to the highest induction dose planned, if needed for a specific patient.

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.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

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

response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (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, (meets protocol specific criteria [see Section 6.1.7 regarding toxicity management]) and/or if the investigator considers them to be adverse events.

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

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (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	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

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.

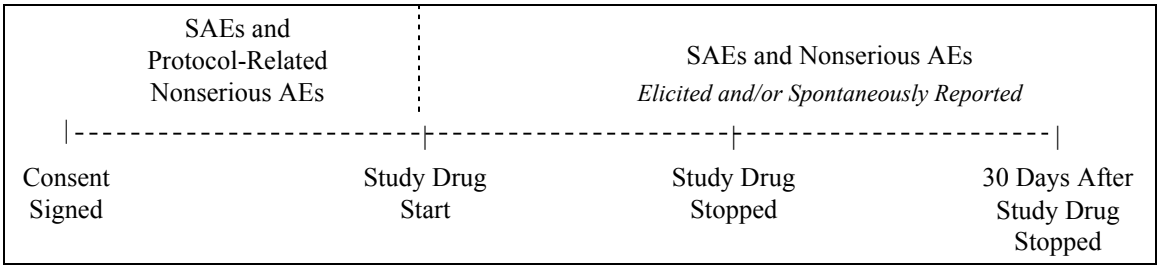
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days, following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

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

Figure 3. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Email:	[redacted]
FAX to:	

For safety concerns, contact the Immunology Safety Team at:

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

Office: [redacted]
Email:

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

Primary Study Designated Physician:

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

Phone: [redacted]

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

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

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

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

Subjects and their partners should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. Male subjects should refrain from donating sperm for up to 30 days post last dose of study drug. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

6.1.7 Toxicity Management

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Re-challenge with study drug may occur once the infection has been successfully treated. If study drug administration is interrupted for more than 10 days, they should notify their study site physician, and the Investigator should consult with the study designated physician about discontinuing the subject from the study. If the subject continues in the study after an interruption > 10 days during the Induction period, he/she will be considered a non-responder and will be censored for efficacy endpoints from that point forward through the end of the study. These subjects will continue to be clinically monitored and will be evaluated in the safety analyses. Subjects who develop active tuberculosis must be withdrawn from the study immediately.

Serious Gastrointestinal Events: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation.

ECG Abnormality: Subjects should be discontinued for an ECG change considered clinically significant.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment and follow any local guidelines. 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, (meets protocol specific criteria [see Section 6.1.7 regarding toxicity management]) and/or if the investigator considers them to be adverse events. Specific toxicity management guidelines for abnormal laboratory values in hemoglobin, absolute neutrophil, absolute lymphocytes, total white blood cell, platelet, liver transaminases, and serum creatinine is described per the table below (confirmation by repeat testing is required).

Hemoglobin	• If confirmed < 8.0 g/dL or decrease from BL > 2.0 g/dL, interrupt study drug dosing until hemoglobin value returns to normal reference range or its Baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1000 cells/mm^3, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Discontinue study drug if confirmed < 500 cells/mm^3.
Absolute lymphocytes counts	• If confirmed < 500 cells/mm^3, interrupt study drug dosing until absolute lymphocytes count returns to normal reference range or its Baseline value.
Total white blood cell count	• If confirmed < 2000 cells/mm^3, interrupt study drug dosing until white blood cell count returns to normal reference range or its Baseline value.
Platelet count	• If confirmed < 50,000 cells/mm^3 interrupt study drug dosing until platelet count returns to > 50,000 cells/mm^3 or its Baseline value.
AST or ALT	• Discontinue study drug if confirmed ALT or AST > 3 × ULN with a Total Bilirubin > 2 × ULN or INR > 1.5. • Discontinue study drug if confirmed ALT or AST > 8 × ULN. • Discontinue study drug if confirmed ALT or AST > 5 × ULN for more than 2 weeks.
Serum Creatinine (sCr)	• If confirmed > ULN and change from BL > 1.5-fold, interrupt study drug dosing until sCr value returns to normal reference range or its Baseline value.

If the subject must undergo elective surgery, the study drug should be interrupted 1 week prior to the surgery. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. The study drug can recommence at least 1 week after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.1.8 Cardiac Adjudication Committee

An independent committee of physician experts in cardiac adjudication will be utilized to assess cardiovascular adverse events in a blinded manner as defined by the Cardiac Adjudication Committee charter.

6.1.9 Independent Data Monitoring Committee

An external Independent Data Monitoring Committee (DMC) comprised of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing studies. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter will be prepared outside of the protocol and will descrive the roles and responsibilities of the DMC members, frequency of data reviews, and relevant safety data to be assessed.

Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

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.

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

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

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an

authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

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

Primary Contact: Alternate Contact:

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

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

- Subject entered into the study even though she/he did not satisfy entry criteria.
- Subject who developed withdrawal criteria during the study and was not withdrawn.
- Subject who received wrong treatment or incorrect dose.
- Subject who received excluded or prohibited concomitant treatment.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analysis Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of ABT-494 versus placebo and to assess the pharmacokinetics (PK) of multiple doses of ABT-494 following oral administration in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to immunomodulators or anti-TNF therapy.

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

Unless otherwise specified, statistical tests will be one-sided significance level of 0.05 for efficacy analyses and two-sided of significance level of 0.05 for all other analyses. A test will be deemed significant if the *P* value rounded to three decimal places is less than or equal to 0.050 unless otherwise specified. The SAS System will be used to perform the statistical analyses.

An interim analysis of the primary and secondary efficacy variables as well as safety and pharmacodynamics biomarker data collected from Baseline through Week 16 will be performed after the last subject randomized into Study M13-740 completes the 16-week double-blind, placebo-controlled induction period in this study (Section 8.1.10). A second interim analysis of the secondary efficacy variables for the double-blind extension period, may be performed after 100% of subjects who were re-randomized at Week 16 completes Week 36 of the double-blind extension period in Study M13-740.

8.1.1 Datasets for Analysis

8.1.1.1 Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (MITT) analysis set includes all randomized subjects who have taken at least one dose of study drug in the double-blind induction period. For the MITT analysis set, subjects are assigned to a treatment group based on the randomization schedule, regardless of the treatment actually received. The MITT population will also be referred as "All Randomized and Treated Subjects." The MITT analysis set will be used for all efficacy analysis for the double-blind induction period and baseline demographic and characteristics analyses.

8.1.1.2 Intent-to-Treat Responder and Non-Responder Analysis Sets

The intent-to-treat responders (ITT-R) and intent-to-treat non-responders (ITT-NR) analysis sets includes all re-randomized subjects in the double-blind extension phase who are responders and non-responders at Week 16, respectively. The clinical responder is defined as: average daily liquid/soft stool frequency at least 30% reduction from Baseline and average daily abdominal pain not worse than Baseline OR average daily abdominal pain at least 30% reduction from Baseline and average daily stool frequency not worse than Baseline. The endoscopic responder is defined as: a SES-CD at least 25% reduction from Baseline.

For the ITT-R and ITT-NR analysis sets, subjects are assigned to a treatment group based on the re-randomization schedule, regardless of the treatment actually received. The ITT-R and ITT-NR analysis sets will be used for all efficacy analysis for the double-blind extension phase.

8.1.1.3 Safety Analysis Set

The safety analysis set consists of all subjects who received at least one dose of study medication. For the safety analysis set, subjects are assigned to a treatment group based on the treatment actually received, regardless the treatment randomized.

8.1.2 Subject Accountability

The number of subjects randomized, the number of subjects who received at least one dose of study drug, the number of subjects who completed the study, and the number of subjects who prematurely discontinued will be calculated overall and for each investigational site by treatment group, as well as for all subjects combined.

8.1.3 Definition of Missing Data Imputation

Missing data will be imputed using one or more of the following methods:

Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit for efficacy measures assessed to impute missing data at later visits.

Non-Responder Imputation (NRI): In NRI analyses, subjects who prematurely discontinue the study prior to endoscopic assessment at Week 12/16 will be considered non-responders with respect to endoscopic remission.

Observed Cases (OC): The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

The stool frequency and abdominal pain scores at an assessment visit (e.g., Week 12, Week 16) will be the average of the daily values reported during the 7 usable days preceding the scheduled assessment visit.

If 7 days daily values are not available, an average will be calculated based on the number of days with available data as follows:

- An average for the most recent 6 days will be calculated if data for only 6 days are available,
- An average for the most recent 5 days will be calculated if data for only 5 days are available,
- An average for the most recent 4 days will be calculated if data for only 4 days are available.

Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit.

If the minimum number of days of diary data (i.e., 4 days for SF and AP) are not available, then the subject's score for that visit will be considered missing and NRI will be used for any endpoints (e.g., clinical remission) relating to data for this visit. Subjects who discontinue prior to Week 16 for any reason will be considered as "not-achieved" for clinical remission endpoint.

Mixed Imputation: Subjects who discontinue prior to Week 16 due to lack of efficacy or adverse events will be considered as "not achieved" for the clinical remission. Subjects who discontinue for other reasons will be categorized according to LOCF.

A subject will be considered a failure for the efficacy analyses at a later time points after the corticosteroid dose has been increased to greater than the dose at Baseline.

8.1.4 Demographics and Baseline Characteristics

Baseline characteristics will be summarized for MITT, and ITT-R and ITT-NR analysis sets.

8.1.4.1 Baseline Characteristics and Treatment Group Comparability

Treatment groups will be compared to assess homogeneity at Baseline with respect to demographic variables such as age, gender, race, height, weight, BMI, race, ethnicity, duration of disease, vital signs (blood pressure, heart rate, and temperature), and planned efficacy assessments such as the CDAI score, average daily Abdominal Pain score, Average daily liquid/soft Stool Frequency, SES-CD and Ulcerated surface subscore, fecal calprotectin level, hs-CRP, fistula closure, IBDQ, WPAI and EQ5D.

Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, and range for each treatment group, and will be compared among treatment groups using analysis of variance (ANOVA) for normally distributed variables and Kruskal-Wallis non-parametric ANOVA for non-normally distributed variables. For other categorical or discrete variables, frequencies and percentages will be computed in each category for each treatment group, as well as for all subjects combined, and will be compared among treatment groups using chi-square test or Fisher's exact test (if 25% of the cells have expected counts less than 5).

8.1.4.2 Medical Histories

Frequencies and relative frequencies (percentages) will also be computed for each treatment group for general medical history items.

8.1.4.3 Prior Therapy and Medications

Prior therapy and medications will include all therapies and medications administered prior to the date of the first dose of study drug. Prior therapy and medication will be

summarized for all randomized subjects who received at least one dose of study drug. No statistical test will be performed.

8.1.4.4 Concomitant Medications

Concomitant drugs will be summarized for all randomized subjects who received at least one dose of study drug. Concomitant drugs will be summarized using the World Health Organization (WHO) Drug Dictionary with frequencies and percentages for each treatment group. In addition, the number and percentage of subjects taking 0, 1, 2, 3, 4, 5, and ≥ 6 medications, as well as the number and percentage of subjects taking at least one medication will be calculated for each treatment group. All medications administered between the date of the first dose of study drug and the date of the last dose of study drug, inclusive, (i.e., all medications starting or ongoing during the time interval) will be included. Thus, all medications with an end date prior to the first study drug dose will be excluded from the summary table. No statistical test will be performed.

A subject who reports two or more uses of the same concomitant medication will be counted only once within each generic name. A subject with concomitant medications with more than one generic name will be counted only once in the overall total.

8.1.5 Subject Disposition and Study Drug Exposure

8.1.5.1 Subject Disposition

The number and percentage of subjects who are enrolled, randomized and received at least one dose of study drug, and the number of subjects who prematurely discontinued and the reason for early termination and the number of subjects who enter the 36-week double-blind extension phase will be summarized by treatment group. Premature discontinuation of study drug will be summarized for each treatment group, as well as for all subjects combined, with frequencies and percentages overall and by reason for discontinuation for all randomized subjects who received at least one dose of study drug. Subjects may have multiple reasons for prematurely discontinuing study drug, but will be counted no more than once for the total ("Any Reason").

8.1.5.2 Study Drug Exposure

Exposure to study drug will be summarized for all subjects who have received at least one dose of study drug. The duration (days) of study drug treatment will be summarized with the mean, standard deviation, median and range for each treatment group. The duration of treatment is defined as the difference between the dates of the first and last doses of the treatment plus 1 day. Study drug compliance of the blinded study drug will be summarized for each treatment group. Compliance is defined as the number of capsules taken (i.e., the difference between the number of capsules dispensed and the number of capsules returned) divided by the number of capsules a subject is supposed to take each day times the length of time that the subject was in the Treatment Phase of the study (i.e., Final/Discontinuation Visit date during Treatment Phase – Day 1 [Baseline] Visit date +1). Subjects with missing data for the number of capsules returned will be excluded from the summary.

8.1.6 Efficacy Analysis

8.1.6.1 Primary Efficacy Variable

The co-primary endpoints are:

1. Proportion of subjects who achieve endoscopic remission at Week 12/16.
2. Proportion of subjects who achieve clinical remission at Week 16.

8.1.6.1.1 Analysis of Primary Endpoint

The comparisons between an ABT-494 treatment group and placebo on the two co-primary efficacy endpoints will be performed using MCPMod approach. Subjects with missing primary endpoint data SES CD at Week 12/16 will be classified as "not achieved" (non-responder imputation [NRI] method) for the endoscopic remission endpoint.

The stool frequency and abdominal pain scores at an assessment visit (e.g., Week 12, Week 16) will be the average of the daily values reported during the 7 usable days preceding the scheduled assessment visit.

If 7 days daily values are not available, an average will be calculated based on the number of days with available data as follows:

- An average for the most recent 6 days will be calculated if data for only 6 days are available,
- An average for the most recent 5 days will be calculated if data for only 5 days are available,
- An average for the most recent 4 days will be calculated if data for only 4 days are available.

If the minimum number of days of diary data (i.e., 4 days for SF and AP) are not available, then the subject's score for that visit will be considered missing and NRI will be used for any endpoints (e.g., clinical remission) relating to data for this visit. Subjects who discontinue prior to Week 16 for any reason will be considered as "not-achieved" for clinical remission endpoint. Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit.

The dose-response relationships among the five ABT-494 treatment groups and placebo group will be characterized for the primary endpoints endoscopic remission at Week 12/16 and clinical remission at Week 16 using MCPMod approach. The following models will be considered: linear, E_{max}, exponential, logistic and sigEmax. The MCPMod approach for trial analysis stage consists of two main steps: MCP and Mod step. The MCP step focuses on establishing evidence for a drug effect across the doses, i.e., detecting a statistically significant dose response signal for the clinical endpoint and patient population investigated in the study. This step will typically be performed using

an efficient test for trend, adjusting for the fact that multiple candidate dose response models are being considered. If a statistically significant dose response signal has been established, one proceeds with determining a reference set of significant dose response models by discarding the non-significant models from the initial candidate set.

The response function will be the log odds (logit) of the proportion of subjects with endoscopic/clinical remission. The fitted curve will be shown graphically with confidence intervals for each dose. Estimates of the treatment differences in the response function and associated 95% confidences for each active dose against placebo will be calculated from the model. These results will be back-transformed to give point estimates of the difference in proportions and associated 95% confidence intervals.

8.1.6.1.2 Sensitivity Analysis of the Primary Efficacy Variable

The following sensitivity analyses for the primary endpoint of endoscopic remission will be conducted:

- A sensitivity analysis using observed cases, which excludes those subjects with missing post-baseline endoscopy, will also be done.

The following sensitivity analyses for the primary endpoint of clinical remission will be conducted:

- An analysis of observed cases, which excludes those subjects with missing SF or AP data at scheduled assessment visits.
- The primary analysis will be repeated using mixed-imputation. Subjects who discontinue prior to Week 16 due to lack of efficacy or adverse events will be considered as "not achieved" for the clinical remission. Subjects who discontinue for other reasons will be categorized according to LOCF.

Subgroup (characterized by the varying inclusion and exclusion criteria) analysis for the primary endpoints, clinical remission and endoscopic remission will be conducted.

8.1.6.2 Secondary Efficacy Variables

8.1.6.2.1 Analysis of Secondary Endpoints

Secondary efficacy variables are divided into two groups. The first group includes double-blind induction treatment period secondary endpoints. Analyses for the first group of secondary endpoints will be performed using MITT analysis set. The second group includes double-blind extension phase secondary endpoints. Analyses for the second group of secondary endpoints will be performed using ITT-N and ITT-NR analysis sets.

For categorical secondary endpoints, the pairwise comparisons for the difference in proportions of subjects between treatment groups will be analyzed using the CMH test adjusted for randomization stratification variable(s), Crohn's disease severity (SES-CD $< 15, \geq 15$) at Baseline and prior anti-TNF use (naïve, experienced). Additionally, the CMH-based 95% confidence interval for the difference in proportions will be provided. The non-responder imputation will be used for subjects with missing data at the endpoint evaluated. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses for the secondary endpoints.

In general, continuous secondary efficacy variables with repeated measurements will be analyzed using a Mixed Effect Repeated Measure (MMRM) model. Continuous secondary efficacy variables will also be analyzed using an Analysis of Covariance (ANCOVA) model including factors for treatment group and stratification variable, Crohn's disease severity (SES-CD $< 15, \geq 15$) at Baseline and prior anti-TNF use (naïve, experienced). Baseline values will be used as a covariate in the MMRM and ANCOVA models. The MMRM analysis is considered primary for inferential purposes.

8.1.6.3 Additional Efficacy Endpoints

8.1.6.3.1 Analysis of Additional Endpoints

The pairwise comparisons for the difference between treatment groups for the additional categorical and continuous endpoints will be analyzed similarly as the secondary endpoints.

8.1.6.4 Multiple Comparisons

The MCP step in MCPMod approach will typically be performed using an efficient test for trend, adjusting for the fact that multiple candidate dose response models are being considered.

8.1.7 Safety Analysis

Adverse events (AEs), laboratory data and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety 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 30 days after the last dose of the study medication. AEs will be summarized separately for: 1) double-blind induction period; 2) double-blind extension phase; 3) over the entire 52-week study duration. An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to early termination (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 15.1 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage. Treatment group differences (each ABT-494 dose group versus placebo group, as well as ABT-494 dose groups combined versus placebo group) in the overall incidence of treatment-emergent AEs will be assessed with Fisher's exact test for each preferred term.

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

8.1.7.1 General Considerations

Safety analyses will be carried out using the safety analysis set, which includes all subjects who receive at least one dose of study medication. Incidence of adverse events, including those related to study drug, changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed.

Treatment-emergent adverse events will be tabulated by system organ class (SOC) and by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term for each treatment group. Mean change from Baseline for laboratory and vital signs data will be summarized.

Missing safety data will not be imputed.

8.1.7.2 Analysis of Adverse Events

8.1.7.2.1 Treatment-Emergent Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent adverse events, defined as AEs that began or worsened in severity after initiation of study drug in each period of the study, will be tabulated by system organ class (SOC) and MedDRA preferred term for each treatment group.

Adverse events starting more than 30 days following discontinuation of study drug will not be included in summaries of treatment-emergent AEs. When summarizing adverse events by relationship or severity, if a subject has an event with unknown severity or relationship then the subject will be counted in the severity/relationship category of "unknown" even if the subject has a second occurrence of the same event with a severity/relationship present. The only exception is if the subject has a second occurrence of the same event with the most extreme severity (i.e., "severe") or a relationship categories of "reasonable possibility." In this case, the subject will be counted under these most extreme severity/relationship categories.

Subjects reporting more than one AE for a given MedDRA preferred term will be counted only once for that term using the most severe incident in each study period. Subjects reporting more than one type of event within an SOC will be counted only once for that SOC.

Frequencies and percentages of subjects with treatment-emergent AEs will be summarized for each treatment group as follows:

- Any event
- By system organ class, and preferred term
- By system organ class, preferred term and maximum relationship
- By system organ class, preferred term and maximum severity
- Any event and by system organ class and preferred term for events resulting in death
- Any event and by system organ class and preferred term for events resulting in study drug discontinuation
- Any event and by system organ class and preferred term for serious events
- Any event and by system organ class and preferred term for adverse events with a relationship of "reasonable possibility"
- Any event and by system organ class and preferred term for adverse events of special interest (infection, opportunistic infection, and gastrointestinal perforations, malignancies and drug related hepatic disorders)

All AEs leading to early termination of study drug will be presented in listing format.

Frequencies and percentages for any AE and for each preferred term will be compared between each of the ABT-494 dosing groups and the placebo group using a Fisher's exact test.

The adverse events of special interest (infection, opportunistic infection, and gastrointestinal perforations, malignancies and drug related hepatic disorders) will be specified in the SAP.

A listing by treatment group of treatment-emergent AEs grouped by SOC and MedDRA preferred term with subject ID numbers will be generated.

The post-treatment AEs will be summarized in the same way as the treatment-emergent AEs described above.

8.1.7.2.2 Serious Adverse Events and Death

All treatment-emergent serious adverse events, adverse events leading to death, and adverse events leading to discontinuation will also be presented in listing format. In addition, SAEs will be summarized by SOC and MedDRA preferred term.

8.1.7.3 Analysis of Laboratory and Vital Sign Data

Changes from Baseline to minimum value, maximum value and final values in continuous laboratory and vital sign parameters will be summarized by treatment group. Treatment group differences between each of the ABT-494 dosing groups and the placebo group for mean changes from Baseline will be analyzed using ANOVA.

Vital signs and laboratory data will be described by statistical characteristics and frequency of abnormal values. Frequencies and percentages of subjects with laboratory shifts from Baseline to the final values using normal ranges to define categories (low, normal, high, and missing) will be summarized by the respective categories. Values beyond the normal values will be listed. Low or high laboratory values will also be flagged in the data listings.

Analysis details will be specified in the SAP.

8.1.8 Pharmacokinetic and Exposure-Response Analyses

Individual ABT-494 plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods.

Data from this study may be combined with data from other studies for the population pharmacokinetic and exposure-response analyses. Population pharmacokinetic and

exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic and exposure-response analyses.

Population pharmacokinetic analyses will be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effects modeling approach with the NONMEM software (Version 7, or a higher version). The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent CL/F and apparent V/F of ABT-494 will be the pharmacokinetic parameters of major interest in the analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models.

1. The objective function of the best model is significantly smaller than the alternative model(s).
2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic of renal function, etc.) will be explored using stepwise forward selection method, or another

suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary pharmacokinetic parameters with various covariates will be explored.

Relationships between ABT-494 exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored. Initially, the time-course of placebo response will be modeled. Subsequently the relationship between exposure (e.g., population pharmacokinetic model predicted average concentrations, AUC, trough concentrations, the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and drug effect will be explored after accounting for the time-course of placebo response. Several classes of models (e.g., linear, log-linear, exponential, E_{max}, sigmoid E_{max}, etc.) will be evaluated to characterize the exposure-response relationship based on the observed data. Results of the pharmacokinetic and exposure-response analyses may be summarized in a separate report prior to regulatory filing of ABT-494 for treatment of Crohn's disease, rather than in the Clinical Study Report.

Additional analyses will be performed if useful and appropriate.

8.1.9 Statistical Analysis of Biomarker Data

Summary statistics for the pharmacodynamic biomarkers and disease response biomarkers at Baseline and post-treatment time points, in addition to change from Baseline at each time will be provided; this will include mean, standard deviation, median, quartiles, and range for each group. Appropriate graphical visualizations such as association of each biomarker to the relevant efficacy endpoints, pairwise correlations between biomarkers,

trellis/3D plots that condition on Baseline factors, etc., will be provided. The pharmacodynamic effect of each biomarker between the placebo and ABT-494 treatment groups will be evaluated via a mixed-effects model with Treatment, Time and Treatment × Time interaction as fixed-effects, the corresponding Baseline score as a covariate, and "subjects nested within the treatment group" as a random-effect. Other Baseline variables such as age, weight, etc., may be considered as appropriate. For biomarkers identified to have significant overall treatment effect via this mixed-effects model analysis, dose response models with the biomarker as a continuous response will be explored. In addition to the above analyses of biomarkers individually, the effect of certain combination of biomarkers on the treatment groups may be explored.

The association of biomarkers to the efficacy and safety endpoints will be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling algorithms. Pairwise correlations and graphical summaries will be provided. Optimal multivariate combinations of biomarkers that associate with efficacy endpoints, subject response/non-response (with respect to appropriate clinical endpoints), and also with safety endpoints will be explored via a variety of statistical predictive modeling algorithms. Also cut-points for individual biomarkers and optimal combinations of biomarkers that differentiate the subject response with respect to efficacy/safety endpoints will be explored. The significance of these multivariate combinations of biomarkers will be assessed via at least 20 iterations of 5-fold cross-validation.

8.1.10 Interim Analysis

An interim analysis of the primary and secondary efficacy variables for the double-blind induction period, as well as safety and pharmacodynamics during the double-blind induction period will be performed using data collected from Baseline through Week 16 after the last subject randomized into this study completes the double-blind induction period in Study M13-740. A second interim analysis of the secondary efficacy, safety and pharmacodynamics variables for the double-blind extension period, may be performed using data collected from Baseline through Week 32 after 50% of subjects who

were re-randomized at Week 16 completes Week 32 of the double-blind extension period in Study M13-740. A database lock will be performed and any discrepant data will be clarified before the lock. The analysis will be conducted by an independent AbbVie statistician who is not part of the ABT-494 Study Team. No alpha adjustment will be made for this Phase 2 study.

8.2 Determination of Sample Size

A total of 210 subjects will be equally allocated to five treatment groups and the placebo group, representing a randomization ratio of 1:1:1:1:1:1. The sample size for this study is based on the expected proportion of subjects who achieve endoscopic remission at Week 12/16 and on the expected proportion of subjects who achieve clinical remission at Week 16. Assuming an endoscopic remission (as well as clinical remission) rate of 12% in the placebo arm and maximum of 35% in at least one of the ABT-494 BID treatment arms (3 mg BID, 6 mg BID, 12 mg BID and 24 mg BID) at Week 12/16, a sample size of 35 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a prespecified set of candidate models, and to estimate target doses of interest (e.g., the minimum effective dose, MED) via modeling using MCP-Mod (Multiple comparison procedure and modeling) approach. This approach provides at least 80% average power to detect a dose effect at 5% level of significance (one-sided) with the linear, E_{max}, exponential, logistic and sigEmax models pre-specified as likely candidates to characterize the dose-response for ABT-494 for the two co-primary endpoints of clinical and endoscopic remission.

9.0 Ethics

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the

ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

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 or any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in

the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

A separate informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional pharmacogenetic, serologic markers, mRNA and gene expression analyses. The nature of the testing should be explained and the subject given an opportunity to ask questions. The separate informed consents must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for optional analysis, it will not impact their participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The following assessments that will be completed by subject will be considered source documentation:

- IBDQ
- EQ-5D
- WPAI-CD
- Abdominal Pain Rating Scale (0 – 10 Scale)

Site staff will verify completion of these forms. All questionnaires must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, the date of the correction, the reason for the correction, and the initials of the study subject who is making the correction. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry.

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

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

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

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

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 maintained and managed by CRF Health.

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

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

10.4 Data Collection Process

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

11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel. This meeting will include a detailed

discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires and Subject Dosing Diary completion, and specimen collection methods.

The AbbVie CRA will monitor each site throughout the study.

Source document verification will be performed.

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

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.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

12.0 Use of Information

All information concerning ABT-494 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 ABT-494. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to 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 study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

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

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, 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 patient 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 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.

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

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

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory 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.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABT-494.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects with Moderately to Severely Active Crohn's Disease who have Inadequately Responded to or are Intolerant to Immunomodulators or Anti-TNF Therapy
Protocol Date:	07 November 2016

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical Pharmacology and Pharmacometrics
		Statistics
		Clinical
		Bioanalysis
		Global Drug Supply Management

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

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

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

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

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

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

   _____HOURS

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

   _____HOURS

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

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

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

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

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

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

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

CIRCLE A NUMBER

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

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

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

CIRCLE A NUMBER

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

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

Appendix E. Standard Weights

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Actual Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
101.6 (40.0)	56.8 (125.3)	56.8 (125.3)
102.9 (40.5)	56.6 (124.8)	56.6 (124.8)
104.1 (41.0)	56.4 (124.3)	56.4 (124.3)
105.4 (41.5)	56.2 (123.8)	56.2 (123.8)
106.7 (42.0)	56.0 (123.0)	56.0 (123.0)
108.0 (42.5)	55.8 (123.0)	55.8 (123.0)
109.2 (43.0)	55.6 (122.7)	55.6 (122.7)
110.5 (43.5)	55.5 (122.4)	55.5 (122.4)
111.8 (44.0)	55.4 (122.1)	55.4 (122.1)
113.0 (44.5)	55.2 (121.8)	55.2 (121.8)
114.3 (45.0)	55.1 (121.6)	55.1 (121.6)
115.6 (45.5)	55.1 (121.4)	55.1 (121.4)
116.8 (46.0)	55.0 (121.3)	55.0 (121.3)
118.1 (46.5)	55.0 (121.2)	55.0 (121.2)
119.4 (47.0)	54.9 (121.1)	54.9 (121.1)
120.7 (47.5)	54.9 (121.1)	54.9 (121.1)
121.9 (48.0)	54.9 (121.1)	40.8 (89.9)
123.2 (48.5)	54.9 (121.1)	41.3 (91.0)
124.5 (49.0)	55.0 (121.2)	41.8 (92.1)
125.7 (49.5)	55.0 (121.3)	42.3 (93.3)
127.0 (50.0)	55.1 (121.5)	42.8 (94.4)
128.3 (50.5)	55.2 (121.7)	43.4 (95.6)
129.5 (51.0)	55.3(121.9)	43.9 (96.8)
130.8 (51.5)	55.4 (122.1)	44.4 (98.0)
132.1 (52.0)	55.5 (122.4)	45.0 (99.2)
133.4 (52.5)	55.7 (122.7)	45.5 (100.4)
134.6 (53.0)	55.8 (123.1)	46.1 (101.6)
135.9 (53.5)	56.0 (123.5)	46.6 (102.8)
137.2 (54.0)	56.2 (123.9)	47.2 (104.1)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Actual Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
138.4 (54.5)	56.4 (124.4)	47.8 (105.3)
139.7 (55.0)	56.7 (124.9)	48.3 (106.6)
141.0 (55.5)	56.9 (125.5)	48.9 (107.9)
142.2 (56.0)	57.2 (126.1)	49.5 (109.1)
143.5 (56.5)	57.4 (126.7)	50.1 (110.4)
144.8 (57.0)	57.7 (127.3)	50.7 (111.7)
146.1 (57.5)	58.1 (128.0)	51.3 (113.0)
147.3 (58.0)	58.4 (128.7)	52.2 (115.0)
148.6 (58.5)	58.7 (129.5)	52.6 (116.0)
149.9 (59.0)	59.1 (130.3)	53.1 (117.0)
151.1 (59.5)	59.5 (131.1)	53.6 (118.3)
152.4 (60.0)	59.9 (132.0)	54.2 (119.5)
153.7 (60.5)	60.3 (132.9)	54.8 (120.8)
154.9 (61.0)	60.7 (133.8)	55.3 (122.0)
156.2 (61.5)	61.1 (134.8)	56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)
158.8 (62.5)	62.1 (137.0)	57.4 (126.5)
160.0 (63.0)	62.6 (138.0)	58.0 (128.0)
161.3 (63.5)	63.0 (139.0)	58.7 (129.5)
162.6 (64.0)	63.5 (140.0)	59.4 (131.0)
163.8 (64.5)	64.1 (141.3)	60.1 (132.5)
165.1 (65.0)	64.6 (142.5)	60.8 (134.0)
166.4 (65.5)	65.2 (143.8)	61.4 (135.5)
167.6 (66.0)	65.8 (145.0)	62.1 (137.0)
168.9 (66.5)	66.4 (146.5)	62.8 (138.5)
170.2 (67.0)	67.1 (148.0)	63.5 (140.0)
171.5 (67.5)	67.8 (149.5)	64.2 (141.5)
172.7 (68.0)	68.5 (151.0)	64.9 (143.0)
174.0 (68.5)	69.2 (152.5)	65.5 (144.5)
175.3 (69.0)	69.8 (154.0)	66.2 (146.0)
176.5 (69.5)	70.5 (155.5)	66.9 (147.5)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Actual Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
177.8 (70.0)	71.2 (157.0)	67.6 (149.0)
179.1 (70.5)	71.9 (158.5)	68.3 (150.5)
180.3 (71.0)	72.6 (160.0)	68.9 (152.0)
181.6 (71.5)	73.4 (161.8)	69.6 (153.5)
182.9 (72.0)	74.1 (163.5)	70.3 (155.0)
184.2 (72.5)	75.0 (165.3)	71.2 (156.9)
185.4 (73.0)	75.7 (167.0)	71.9 (158.5)
186.7 (73.5)	76.6 (169.0)	72.6 (160.2)
188.0 (74.0)	77.5 (171.0)	73.4 (161.8)
189.2 (74.5)	78.4 (172.8)	74.1 (163.4)
190.5 (75.0)	79.1 (174.5)	74.9 (165.1)
191.8 (75.5)	80.2 (176.8)	75.6 (166.8)
193.0 (76.0)	81.2 (179.0)	76.4 (168.4)
194.3 (76.5)	82.0 (180.8)	77.2 (170.1)
195.6 (77.0)	82.9 (182.9)	77.9 (171.8)
196.9 (77.5)	83.9 (185.0)	78.7 (173.5)
198.1 (78.0)	84.9 (187.2)	79.5 (175.2)
199.4 (78.5)	85.9 (189.4)	80.3 (177.0)
200.7 (79.0)	86.9 (191.6)	81.0 (178.7)
201.9 (79.5)	87.9 (193.9)	81.8 (180.5)
203.2 (80.0)	89.0 (196.2)	82.6 (182.2)
204.5 (80.5)	90.0 (198.6)	*Height in shoes with one inch heels
205.7 (81.0)	91.1 (200.9)	*Indoor clothing weighing 5 pounds for men and 3 pounds for women
207.0 (81.5)	92.2 (203.3)	*Centimeters × 0.3937 = inches
208.3 (82.0)	93.3 (205.8)	*Pounds × 0.4535 = kilograms

Appendix F. SES-CD Scoring

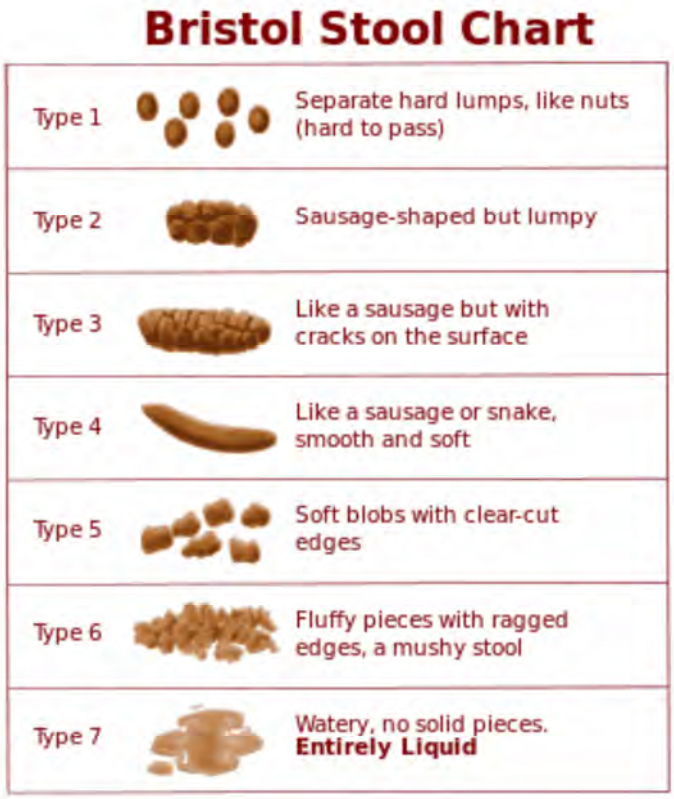
	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total
Size of Ulcers Enter: 0 if none 1 if aphthous ulcers (Ø 0.1 to 0.5 cm) 2 if large ulcers (Ø 0.5 to 2 cm) 3 if very large ulcers (Ø > 2 cm)						
Ulcerated Surface Enter: 0 if none 1 if < 10% 2 if 10% – 30% 3 if > 30%						
Affected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

Appendix G. Latent TB Risk Factor Questionnaire Example

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
   - Sub-Saharan Africa
   - India
   - China
   - Mexico
   - Southeast Asia or Micronesia
   - The former Soviet Union
3. Have you lived or worked in a prison, homeless shelter, immigration center, or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
   - Chronic cough
   - Production of sputum
   - Blood-streaked sputum
   - Unexplained weight loss
   - Fever
   - Fatigue/tiredness
   - Night sweats
   - Shortness of breath

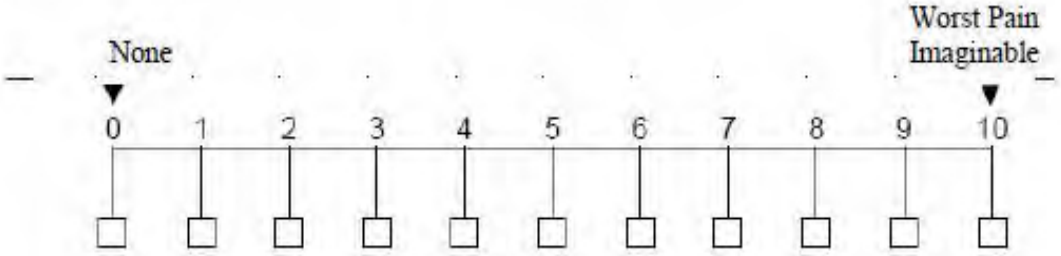
Available from: http://www.mayoclinic.com/health/tuberculosis/DS00372/DSECTION=risk-factors and http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix H. Bristol Stool Chart



Appendix I. Abdominal Pain Rating Scale (0 – 10 Scale)

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



0 None – No symptoms.

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

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

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

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

Appendix J. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Methodology:
Seventeenth paragraph, last bullet previously read:

An optional biopsy for Gene expression sub-study will be collected during colonoscopy at/during Screening, and at Week 12/16 for approximately 70 subjects in the study.

Has been changed to read:

An optional biopsy for Gene expression sub-study will be collected during colonoscopy at/during Screening, and at Week 12/16 for approximately 80 subjects in the study.

Section 5.1 Overall Study Design and Plan: Description
Subsection Follow-Up Period
Last paragraph
Add: new second sentence

The 10 day window for subject rollover may be extended on a case by case basis after consultation with the medical monitor.

Section 5.2.1 Inclusion Criteria
Criterion 9 and 10 previously read:

9. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 180 days after the last dose of study drug.
10. Male subjects who are sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 90 days after the last dose of study drug to practice the protocol-specified contraception (refer to Section 5.2.4).

Has been changed to read:

9. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
10. Male subjects who are sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 30 days after the last dose of study drug to practice the protocol-specified contraception (refer to Section 5.2.4).

Section 5.2.3.1 Prior Therapy
Delete: second paragraph

If subjects have/had ever been treated with corticosteroid, immunosuppressant or aminosalicylates, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment will be recorded in appropriated eCRF. The details of dates of administration and dosages will be also recorded within the past 90 days.

Section 5.2.3.1 Prior Therapy
Third paragraph
Add: new last sentence

Subjects who have not been exposed to an anti-TNF will have their immunosuppressants recorded beyond the past 90 days.

Section 5.2.4 Contraceptive Recommendations
Subsection <u>Contraception Recommendation for Females</u>
Second paragraph, last bullet previously read:

Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

Has been changed to read:

Age < 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 mIU/mL.

Section 5.2.4 Contraceptive Recommendations
Subsection Contraception Recommendation for Females
Third paragraph previously read:

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered a woman of childbearing potential and is required to practice at least one of the following highly effective method of birth control, on Study Day 1 (or earlier) through at least 30 days (180 days for subjects taking MTX) after the last dose of study drug.

Has been changed to read:

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered a woman of childbearing potential and is required to practice at least one of the following highly effective method of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

Section 5.2.4 Contraceptive Recommendations
Subsection Contraception Recommendation for Females
Add: new last paragraph

It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy ABT-494. The concomitant methotrexate (MTX) that may have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant MTX and that duration of contraception after discontinuation of the MTX should be based on the local label.

Section 5.2.4 Contraceptive Recommendations
Subsection Contraception Recommendation for Males
Second paragraph previously read:

A male subject who is sexually active with female partner(s) of childbearing potential, must agree from Study Day 1 through 90 days after the last dose of study drug to practice contraception with:

Has been changed to read:

A male subject who is sexually active with female partner(s) of childbearing potential, must agree from Study Day 1 through 30 days after the last dose of study drug to practice contraception with:

Section 5.2.4 Contraceptive Recommendations
Subsection Contraception Recommendation for Males
Second paragraph, first bullet
Add: new second paragraph

OR

Section 5.2.4 Contraceptive Recommendations
Subsection Contraception Recommendation for Males
Third paragraph previously read:

Additionally, male subject agrees not to donate sperm from Study Day 1 through 90 days after the last dose of study drug.

Has been changed to read:

Additionally, male subject agrees not to donate sperm from Study Day 1 through 30 days after the last dose of study drug.

Section 5.2.4 Contraceptive Recommendations
Subsection <u>Contraception Recommendation for Males</u>
Add: new last paragraph

It is important to note that contraception and sperm donation recommendations described above are specifically intended to prevent pregnancy during and after exposure to the investigational therapy ABT-494. The concomitant methotrexate (MTX) that may have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant MTX and that duration of contraception and the requirement not to donate sperm after discontinuation of the MTX should be based on the local label.

Section 5.3.1.6 Collection of Samples for Gene Expression
First sentence previously read:

Optional gene expression samples may be evaluated in approximately 70 subjects.

Has been changed to read:

Optional gene expression samples may be evaluated in approximately 80 subjects.

Section 5.3.6.3 Gene Expression Variables
First paragraph, first sentence previously read:

For patients who consent to this optional testing, gene expression may be evaluated in approximately 70 subjects.

Has been changed to read:

For patients who consent to this optional testing, gene expression may be evaluated in approximately 80 subjects.

Section 6.1.3 Relationship to Study Drug
In-text table previously read:

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.

Has been changed to read:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

Section 6.1.6 Pregnancy
Last paragraph, second sentence previously read:

Male subjects should refrain from donating sperm for up to 90 days post last dose of study drug.

Has been changed to read:

Male subjects should refrain from donating sperm for up to 30 days post last dose of study drug.

Section 8.1 Statistical and Analysis Plans
Last paragraph, last sentence previously read:

A second interim analysis of the secondary efficacy variables for the double-blind extension period, may be performed after 50% of subjects who were re-randomized at Week 16 completes Week 32 of the double-blind extension period in Study M13-740.

Has been changed to read:

A second interim analysis of the secondary efficacy variables for the double-blind extension period, may be performed after 100% of subjects who were re-randomized at Week 16 completes Week 36 of the double-blind extension period in Study M13-740.

Section 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
Second paragraph, last sentence previously read:

The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Has been changed to read:

The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Section 10.1 Source Documents
First paragraph
Add: new fourth and fifth sentence

The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

Section 13.0 Completion of the Study
Third paragraph, first sentence previously read:

The investigator must retain any records related to the study according to local requirements.

Has been changed to read:

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements.