1.0 Title Page

Clinical Study Protocol M14-431

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy

Incorporating Administrative Changes 1 and 2, and Amendments 1, 2, 3, 4, 5, 6, and 7

AbbVie Investigational Product:	Upadacitinib (ABT-494)
Date:	05 March 2021
Development Phase:	3
Study Design:	A randomized, double-blind, placebo-controlled induction study
EudraCT Number:	2017-001226-18
Investigators:	Multicenter Trial (Investigator information is on file at AbbVie)
Sponsor:	**For Non-EU Countries, Excluding Japan:** AbbVie 1 North Waukegan Road Bldg. AP31-2 North Chicago, IL 60064 **For Japan:** AbbVie GK 3-1-21, Shibaura, Minato ku Tokyo 108-0023, Japan **For EU Countries:*** AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	01 June 2017
Amendment 1	02 October 2017
Amendment 2	24 January 2018
Amendment 2.01 (Canada Only)	16 May 2018
Amendment 2.02 (Hungary Only)	06 June 2018
Amendment 3	24 August 2018
Administrative Change 1	19 September 2018
Amendment 3.01 (Canada Only)	11 October 2018
Amendment 3.02 (Hungary Only)	11 October 2018
Amendment 4	08 April 2019
Amendment 4.01 (Canada Only)	03 May 2019
Amendment 4.02 (Hungary Only)	08 May 2019
Amendment 4.03 (China Only)	01 May 2019
Amendment 5	29 April 2020
Administrative Change 2	11 June 2020
Amendment 5.01 (Canada Only)	23 June 2020
Amendment 5.02 (Hungary Only)	23 June 2020
Amendment 5.03 (China Only)	23 June 2020
Amendment 6	24 September 2020
Amendment 6.01 (Canada Only)	02 December 2020
Amendment 6.02 (Hungary Only)	30 November 2020
Amendment 6.03 (China Only)	19 November 2020

The purpose of this amendment is to:

- Update Section 5.1, Section 5.2, Section 5.5.3, Section 5.6.1, and Section 8.2 to decrease the sample size of Part 2 from approximately 150 subjects to approximately 130 subjects, and consequently the total sample size from 645 to 625 subjects.

  Rationale: *An adequate number of subjects to be enrolled in the maintenance study will be achieved with a smaller sample size in Part 2.*
- Update Section 5.1 to increase the maximum percentage of subjects enrolled who have had inadequate response or intolerance to 3 or more biologics from 30% to 35%.

  ***Rationale*:** *To revise the maximum percentage of subjects with an inadequate response or intolerance to 3 or more biologics based on enrollment and updated study sample size.*
- Update Section 1.2, Synopsis.

  Rationale: *To be consistent with Amendment 7 revisions.*
- Update Section 1.2, Synopsis to delete duplicated text for multiple testing procedure and overall type-1 error control from statistical methods.

  Rationale: *To correct a typographical error.*
- Update Section 1.2, Synopsis to add text that details for handling of missing data due to COVID-19 will be described and documented in the statistical analysis plan.

  Rationale: *To align with language in Section 8.1 for COVID-19 modifications for statistical and analytical plans.*
- Update Section 6.1.5 to revise safety team contact information.

  Rationale: *To correct per current safety team contact information.*
- Update Section 8.1 to revise text to "extent" of missing data due to COVID-19.

  Rationale: *To clarify the impact of missing data due to COVID-19 on the efficacy analysis.*
- Update Appendix B, to revise the protocol signatories.

  Rationale: *To update due to personnel changes for this protocol amendment.*
- Remove Appendix K, Protocol Amendment List of Changes.

Rationale: *Appendix was removed from the AbbVie protocol template.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-431
Name of Study Drug: Upadacitinib (ABT-494)	**Phase of Development:** 3
Name of Active Ingredient: Upadacitinib (ABT-494)	**Date of Protocol Synopsis:** 05 March 2021
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy	
Objective: The objective of Study M14-431 is to evaluate the efficacy and safety of upadacitinib compared to placebo as induction therapy in subjects with moderately and severely active Crohn's disease (CD).	
Investigators: Multicenter	
Study Sites: Approximately 400 sites worldwide.	
Study Population: Males and females between 18 and 75 years of age (or minimum age of adult consent according to local regulations) with a confirmed diagnosis of CD for at least 3 months and moderately to severely active CD who have inadequately responded to or are intolerant to biologic therapy. Moderately to severely active CD is defined by: • Average daily very soft or liquid stool frequency (SF) ≥ 4 **AND/OR** average daily abdominal pain (AP) score ≥ 2 (values represent the unweighted daily averages of the corresponding subscores from the Crohn's Disease Activity Index [CDAI]); and • Evidence of mucosal inflammation, defined as Simplified Endoscopic Score for CD (SES-CD) ≥ 6 (≥ 4 for subjects with isolated ileal disease), excluding the presence of narrowing component. Subjects must have had an inadequate response or intolerance to one or more biologic agents for CD (adalimumab, certolizumab, infliximab, ustekinumab and/or vedolizumab). The study will allow enrollment of up to 35% of subjects who have demonstrated inadequate response or intolerance to 3 or more biologics.	
Number of Subjects to be Enrolled: Approximately 625 subjects worldwide.	
Methodology: Study M14-431 is a Phase 3, randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib, an orally administered Janus kinase 1 inhibitor, in adult subjects with moderately to severely active CD who have inadequately responded to or are intolerant to biologic therapy. Subjects who consent and meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into this study, which encompasses 3 parts: (Part 1) a randomized, double-blind, placebo-controlled induction; (Part 2) an open-label, single-arm active induction; and (Part 3) an Extended Treatment Period for non-responders from Part 1 or Part 2.	

Methodology (Continued):

Study visits may be impacted due to the coronavirus disease – 2019 (COVID-19) pandemic or any state of emergency or pandemic situation. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others may be performed. Additional details are provided in the subsequent sections. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Part 1

In Part 1, subjects (n = 495) will be randomized in a 2:1 ratio to upadacitinib 45 mg once daily (QD) or matching placebo for 12 weeks. The randomization will be stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologic treatments (> 1 and ≤ 1). The data collected from subjects from Part 1 will be used for the primary efficacy analysis.

Visits during the study will occur at Baseline and Weeks 2, 4, 8, and 12/Premature Discontinuation (PD) to collect clinical, endoscopic, and laboratory assessments of disease activity.

At Week 12, subjects achieving clinical response, defined as ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) may be eligible to enter the 52-week, double-blind, maintenance portion of Study M14-430.

All subjects who do not achieve clinical response at Week 12 will be able to enroll in Part 3 (Extended Treatment Period) and receive double-blind upadacitinib until Week 24/PD.

Subjects are not eligible to enter Study M14-430 until the ileocolonoscopy procedure at Week 12 has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, the subject can enroll in Study M14-430 if clinical response was achieved at Week 12.

Part 2

Part 2 is an open-label portion (open-label cohort) of this study. Once enrollment in Part 1 is complete, approximately 130 subjects will be enrolled in Part 2 to receive open-label upadacitinib 45 mg QD for 12 weeks. The objective of Part 2 is to have a sufficient number of subjects with clinical response to be rerandomized in the double-blind, maintenance portion of Study M14-430, while minimizing unnecessary exposure to placebo. The data collected from subjects from Part 2 will not be part of the primary efficacy analysis for this study, will use descriptive statistics, and will be reported separately in the clinical study report.

Visits during the study will occur at Baseline and Weeks 2, 4, 8, and 12/PD to collect clinical, endoscopic, and laboratory assessments of disease activity.

At Week 12, subjects achieving clinical response may be eligible to enter Study M14-430. Subjects who do not achieve clinical response at Week 12 will be eligible to participate in Part 3 (Extended Treatment Period) to receive open-label upadacitinib 30 mg QD until Week 24/PD.

Part 3

Part 3 is a 12-week Extended Treatment Period consisting of 3 cohorts of subjects who do not achieve clinical response at Week 12 in Part 1 or Part 2. The objectives of Part 3 are to offer blinded upadacitinib induction treatment to placebo non-responders from Part 1 and to evaluate delayed clinical response to upadacitinib in subjects who did not initially respond to upadacitinib during Part 1 or Part 2.

Methodology (Continued):

- **Cohort 1:** Subjects who received placebo in Part 1 and did not achieve clinical response at Week 12 are eligible to receive double-blind induction treatment with upadacitinib 45 mg QD for 12 weeks (until Week 24).
- **Cohort 2:** Subjects who received double-blind upadacitinib in Part 1 and did not achieve clinical response at Week 12 are eligible to receive double-blind upadacitinib 30 mg QD for 12 weeks (until Week 24).
- **Cohort 3:** Subjects who received open-label upadacitinib during Part 2 and did not achieve clinical response at Week 12 are eligible to receive open-label upadacitinib 30 mg QD for 12 weeks (until Week 24).

Subjects in Cohort 1 and 2 will remain blinded to treatment to avoid unmasking the treatment received during Part 1. The data collected from subjects from Part 3 will not be part of the primary efficacy analysis for this study, will use descriptive statistics, and will be reported separately in the clinical study report.

Subjects are not eligible to enter in Part 3 until the Week 12 endoscopy has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, and the subject has not achieved clinical response, the subject can enter Part 3 of Study M14-431. Visits will occur at Weeks 16, 20 and 24/PD to collect clinical, endoscopic, and laboratory assessments of disease activity.

During Part 3, subjects with persistent symptoms or worsening of CD may be discontinued at any time.

At Week 24, subjects who achieve clinical response may be eligible to enter Study M14-430. Subjects are not eligible to enter Study M14-430 until the ileocolonoscopy procedure at Week 24 for evaluation of mucosal inflammation has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, the subject can enroll in Study M14-430 if clinical response was achieved at Week 24.

Subjects who do not achieve clinical response at Week 24 will be discontinued from Study M14-431 and will receive standard of care treatment at the investigator's discretion. Subjects who do not achieve clinical response at Week 24 and all subjects who prematurely discontinue the study will have a follow-up visit 30 days from the last dose of study drug to collect information on new or ongoing adverse events (AEs) and laboratory assessments. Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the investigator.

The duration of the study could be up to 33 weeks, including Screening Period (5 weeks), a 12-week double-blind or open-label cohort Induction Period (Part 1 and Part 2), a 12-week Extended Treatment Period (Part 3), and a 30-day follow-up for subjects who do not enroll into Study M14-430.

At the Screening Visit, all subjects will be provided with an electronic diary. Subjects will be instructed and trained on how to record CD-related symptoms (including total and very soft and liquid number of stools and abdominal pain), general well-being and use of anti-diarrheals on a daily basis; and use of medications for endoscopy preparation throughout the study. The very soft and liquid stools are defined as consistency Type 6 or Type 7 based on the Bristol Stool Chart.

Methodology (Continued):

The diary will be reviewed by site personnel with the subject at each visit and for the assessment of the clinical endpoints. At each Study Visit, routine physical examination including evaluation of vital signs, extra intestinal manifestations, and presence or absence of fistulas; calculation of CDAI score, average daily very soft or liquid SF and average daily AP (SF and AP entries from the most recent 7-day period prior to each study visit will be used); monitoring of AEs; reporting of concomitant medications and laboratory assessments will be performed. The very soft or liquid SF and AP score values represent the unweighted daily averages of the corresponding subscores from the CDAI. Additionally, subjects will complete quality of life (QoL), CD symptoms, symptoms impact on QoL, and work productivity questionnaires throughout the study.

Subjects will undergo a full colonoscopy (ileocolonoscopy) for evaluation of mucosal inflammation using the SES-CD. All endoscopies will be centrally read to document eligibility at Screening and for Week 12 and 24/PD assessments. Intestinal biopsies during the endoscopic evaluation will be collected for histologic assessment and exploratory research during endoscopy visits at Screening, Week 12, and Week 24/PD in approximately 200 subjects (intestinal biopsy substudy).

Optional blood samples will be collected for exploratory research at Baseline, Week 4, Week 12, and Week 24/PD. Optional stool collections will be done at Baseline, Week 4 and Week 12 for exploratory evaluation of biomarkers in approximately 200 subjects (fecal biomarker substudy).

Concomitant CD-Related Medications (Antibiotics, Aminosalicylates, and/or Methotrexate)

All subjects receiving a stable dose of CD-related antibiotics, aminosalicylates, or methotrexate (MTX) at Baseline should maintain their concomitant treatments without dose changes through the end of the study. Initiating and/or changing doses of these medications are prohibited during the study. Doses of CD-related antibiotics, aminosalicylates, or MTX may be decreased only in the event of safety or tolerability issues.

Concomitant Corticosteroids

Subjects who enter the study on oral corticosteroids are not allowed to change the corticosteroid dose during the first 4 weeks of the induction treatment period. Dose may be decreased only for safety or tolerability issues. Initiating locally acting (rectal or suppository) or systemic corticosteroids is prohibited during the induction treatment period.

At Week 4, subjects who are on prednisone (or oral equivalent) or oral budesonide must have their corticosteroid dose tapered, according to the tapering schedule.

Subjects who do not achieve clinical response at Week 12 in Part 1 or Part 2, and enter Part 3 without having completed the steroid taper should resume the corticosteroid taper at Week 16, according to the tapering schedule.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, as determined by the investigator, must be available.
2. SES-CD (excluding the presence of narrowing component) ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), as confirmed by a central reader.
3. Average daily very soft or liquid SF ≥ 4.0 **AND/OR** average daily AP score ≥ 2.0 at Baseline.
4. Demonstrated an inadequate response or intolerance to one or more of the following biologic agents:
   - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at Baseline and Weeks 2, and 6),
   - At least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous [SC] dose at Baseline, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Baseline, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
   - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Baseline and Weeks 2, and 4),
   - At least one 6-week induction regimen of vedolizumab (300 mg IV at Baseline and Weeks 2, and 6),
   - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8],
   - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics,
   - Intolerance to a biologic may include, but not limited to infusion-related reaction, rash, serum sickness, anaphylaxis, elevated liver enzymes, demyelination, congestive heart failure, infection. Demonstration of intolerance requires no minimum dose or duration of use.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

<u>Concomitant Medications and Treatments</u>

2. Subject on CD related antibiotics who:
   - has not been on stable doses of these medications for at least 14 days prior to Baseline, or
   - has discontinued these medications within 14 days of Baseline.
3. Subject on oral aminosalicylates who:
   - has not been on stable doses of these medications for at least 14 days prior to Baseline, or
   - has discontinued these medications within 14 days of Baseline.
4. Subject on corticosteroids who meet the following:
   - prednisone or equivalent dose > 30 mg/day; or
   - budesonide > 9 mg/day; or
   - has not been on the current course for at least 14 days prior to Baseline and on a stable dose for at least 7 days prior to Baseline.

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

Main Exclusion (Continued):

5. Subject on MTX who:
   - has not been on the current course for ≥ 42 days prior to Baseline, and
   - has not been on a stable dose for ≥ 28 days prior to Baseline

CD Related

6. Subject with the ongoing following known complications of CD:
   - abscess (abdominal or peri-anal),
   - symptomatic bowel strictures,
   - > 2 entire missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum,
   - fulminant colitis,
   - toxic megacolon,
   - or any other manifestation that might require surgery while enrolled in the study.
7. Subject with ostomy or ileoanal pouch
8. Subject diagnosed with conditions that could interfere with drug absorption including but not limited to short gut or short bowel syndrome.
9. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of > 3 bowel resections

Safety

10. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) > 2.0 × upper limit of the reference range (ULN);
    - Total white blood cell count < 2500/μL;
    - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 mL/min/1.73 m^2;
    - Hemoglobin < 9 g/dL;
    - Platelet count < 100,000/μL;
    - Absolute neutrophil count < 1200/μL;
    - Absolute lymphocyte count < 750/μL.

Investigational Products:	Upadacitinib (ABT-494)
Doses:	Part 1: upadacitinib 45 mg QD Part 2: upadacitinib 45 mg QD Part 3: upadacitinib 45 mg QD or upadacitinib 30 mg QD
Mode of Administration:	Oral
Reference Therapy:	Part 1: placebo
Doses:	N/A
Mode of Administration:	Oral

Duration of Treatment: 12 weeks for subjects achieving clinical response at Week 12; or 24 weeks for subjects who do not achieve clinical response at Week 12.

Criteria for Evaluation:

Endpoint Definitions:

- **Clinical remission per patient reported outcomes (PROs):** average daily very soft or liquid SF ≤ 2.8 AND average daily AP score ≤ 1.0 and both not greater than baseline
- **Clinical remission per CDAI:** CDAI < 150
- **Enhanced Clinical Response:** ≥ 60% decrease in average daily very soft or liquid SF and/or ≥ 35% decrease in average daily AP score and both not greater than baseline, or clinical remission
- **Clinical response 100 (CR-100):** Decrease of at least 100 points in CDAI from Baseline
- **Clinical response:** ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP score and both not greater than baseline
- **Endoscopic remission:** SES-CD ≤ 4 and at least 2 point reduction from Baseline and no subscore > 1 in any individual variable, as scored by central reviewer
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline of the induction study (or for subjects with an SES-CD of 4 at Baseline, at least a 2-point reduction from Baseline), as scored by central reviewer

Efficacy:

The co-primary and ranked secondary endpoints will be analyzed separately for EU/EMA and US/FDA regulatory purposes. These endpoints are specified separately for each set of analyses.

EU/EMA Endpoints

Co-primary Endpoints:

1. Proportion of subjects with clinical remission per PROs at Week 12, and
2. Proportion of subjects with endoscopic response at Week 12.

Ranked Secondary Endpoints:

1. Proportion of subjects with clinical remission per CDAI (CDAI < 150) at Week 12
2. Proportion of subjects with clinical remission per PROs at Week 4
3. Proportion of subjects with endoscopic remission at Week 12
4. Proportion of subjects who discontinue corticosteroid use for CD and achieve clinical remission at Week 12, in subjects taking corticosteroids for CD at Baseline
5. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue at Week 12
6. Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 12
7. Proportion of subjects achieving CR-100 at Week 2
8. Proportion of subjects achieving CR-100 at Week 12
9. Proportion of subjects with hospitalizations due to CD at during the 12 week double-blind induction period
10. Proportion of subjects with resolution of extra-intestinal manifestation (EIM) at Week 12, in subjects with EIM at Baseline.

Criteria for Evaluation (Continued):

US/FDA Endpoints

Co-primary Endpoints:

1. Proportion of subjects with clinical remission per CDAI (CDAI < 150) at Week 12, and
2. Proportion of subjects with endoscopic response at Week 12.

Ranked Secondary Endpoints:

1. Proportion of subjects with clinical remission per PROs at Week 12
2. Proportion of subjects with endoscopic remission at Week 12
3. Proportion of subjects who discontinue corticosteroid use for CD and achieve clinical remission per CDAI at Week 12, in subjects taking corticosteroids for CD at Baseline
4. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue at Week 12
5. Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 12
6. Proportion of subjects achieving CR-100 at Week 2
7. Proportion of subjects achieving CR-100 at Week 12
8. Proportion of subjects with clinical remission per CDAI at Week 4
9. Proportion of subjects with hospitalizations due to CD at during the 12-week double-blind induction period
10. Proportion of subjects with resolution of extra-intestinal manifestation (EIM) at Week 12, in subjects with EIM at Baseline.

Additional endpoints are outlined in the protocol.

Pharmacokinetic: Upadacitinib plasma concentrations will be determined from samples collected at each visit beginning at Week 2. Blood samples at the Week 4 visit will be collected prior to dosing if possible. For all other visits, blood samples will be collected at any time during the visit.

Safety: Safety analyses will be performed on the safety set, which includes all subjects who receive at least one dose of study drug. The incidence of AEs, changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study. Electrocardiograms will be performed at screening, and at the end of each Part 1, 2, 3 of the study. AEs and laboratory data, when available, will be graded as described in the National Cancer Institute Common Terminology Criteria for Adverse Events and summarized accordingly.

An external, independent Data Monitoring Committee will be responsible for monitoring unblinded safety data and alerting AbbVie to possible safety concerns related to the conduct of the study.

Exploratory Research Variables (Optional Serum, Whole Blood, Stool and Biopsy Samples): Prognostic, surrogate, predictive, and pharmacodynamic biomarker signatures may be investigated. Samples for different applications including, but not limited to, pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomic, metagenomic, and targeted investigations will be collected at various time points. Optional serum and whole blood collections will be done at Baseline, Week 4, Week 12, and Week 24/PD for evaluation of biomarkers. Optional stool collections will be done at Baseline, Week 4 and Week 12 for exploratory evaluation of biomarkers. Biopsies include optional samples at Screening, Week 12, and Week 24/PD. Assessments will include but may not be limited to nucleic acids, proteins, metabolites, or lipids.

Statistical Methods:

Efficacy: The co-primary endpoints are the proportion of subjects with clinical remission per PROs (EU/EMA) or clinical remission per CDAI (US/FDA) at Week 12 and the proportion of subjects with endoscopic response at Week 12. This study will evaluate one induction dose of upadacitinib 45 mg QD.

Efficacy analysis will be based on all intent-to-treat (ITT) subjects. The ITT analysis set includes all randomized subjects who have taken at least one dose of study drug in the double-blind induction period from Part 1.

The comparison between treatment groups on the co-primary efficacy endpoints will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by Baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologics used (> 1 and ≤ 1). Both of the co-primary efficacy endpoints will be tested at two-sided significance level of 0.05. A CMH-based, two-sided 95% confidence interval for the difference between treatment groups will be calculated. If the average daily SF or average daily AP score (EU/EMA) or CDAI (US/FDA) data at Week 12 are missing, the non-responder imputation approach will be applied for the clinical remission per PROs and clinical remission per CDAI endpoints, respectively. Subjects who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for clinical remission or endoscopic response endpoints.

A multiple testing procedure will be used to provide strong control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses with respect to the co-primary endpoints, and ranked secondary endpoints. Specifically, testing will utilize a sequence of hypothesis testing for the co-primary endpoints followed by the ranked secondary endpoints, and will begin with testing co-primary endpoints using α of 0.05 (2-sided). If both co-primary endpoints achieve statistical significance, continued testing will follow a pre-specified weight of α allocation between individual hypotheses as well as between families of hypotheses. The details of the testing procedure will be specified and documented in the statistical analysis plan (SAP).

In general, continuous secondary efficacy variables with repeated measurements will be analyzed using a Mixed Effect Repeated Measure (MMRM) model. Continuous secondary efficacy variables which are collected at only one post-baseline visit (such as SES-CD) will be analyzed using an Analysis of Covariance (ANCOVA) model. Categorical secondary efficacy variables will be analyzed using the CMH test controlling for stratification variables. NRI for missing data will be used for categorical secondary endpoints.

The extent of missing data due to COVID-19 will be monitored and appropriate analysis to handle these missing data may be performed; details will be included in the SAP. Further details of the statistical analysis will be described and documented in the SAP.

Statistical Methods (Continued):

Pharmacokinetic: 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 for upadacitinib oral clearance and volume of distribution. Additional parameters may be estimated if useful in the interpretation of the data. Data from this study may be combined with data from other studies for the population pharmacokinetic analyses.

Safety: AEs, laboratory data, and vital signs are the primary safety parameters in this study. All safety comparisons will be performed between treatment groups using the safety set. Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 30 days after the last dose of the study drug for subjects who do not participate in Study M14-430, or within 30 days after the last dose of study drug in Study M14-431 or first dose of study drug in Study M14-430 if the subject enrolls in Study M14-430, whichever comes first.

An overview of treatment-emergent AEs, including AEs of special interest, AEs leading to death, AEs leading to PD, AEs by Medical Dictionary for Drug Regulatory Activities preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

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

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-mercaptopurine
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANC	absolute neutrophil count
AP	abdominal pain
AST	aspartate transaminase
AUC	area under the concentration-time curve
AZA	Azathioprine
BCG	Bacille Calmette-Guérin
BID	twice daily
BP	blood pressure
CAC	Cardiovascular Adjudication Committee
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CD4, CD8	cluster of differentiation
CGC	common gamma-chain
CGHAS/IGHAS	Colonic and Ileal Global Histologic Disease Activity Score
CL/F	oral clearance
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
C_{min}	minimum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRP	C-reactive protein
CSS	Crohn's Symptoms Severity Questionnaire

CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTP	direct to patient
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EIM	extra-intestinal manifestations
EMA	European Medicines Agency
E_{max}	maximum effect
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Levels
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FCP	fecal calprotectin
FSH	follicle-stimulating hormone
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
Hct	Hematocrit
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
HIV Ab	human immunodeficiency virus antibody
hs-CRP	high-sensitivity C-reactive protein
IBDQ	Inflammatory Bowel Disease Questionnaire
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IL-6R	interleukin-6 receptor
IM	Intramuscular
INF-g	interferon gamma
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IV	Intravenous
JAK	Janus kinase
LDL-C	low density lipoprotein cholesterol
lncRNA	long non-coding RNA
MACE	major adverse cardiac event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNA
MMRM	Mixed-Effect Model Repeated Measure
MTX	Methotrexate
NCI	National Cancer Institute
NK	natural killer
NMSC	nonmelanoma skin cancer
NOEL	no observed effect level
NRI	non-responder imputation
NSAIDs	nonsteroidal anti-inflammatory drugs
OC	observed cases
PCR	polymerase chain reaction
PD	premature discontinuation
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
piRNA	piwi interacting RNA
PK	Pharmacokinetic
PPD	purified protein derivative

PRO	patient reported outcome
QD	once daily
QoL	quality of life
QTcF	Fridericia's correction formula
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SES-CD	Simplified Endoscopic Score for Crohn's Disease
SF	stool frequency
SF-36	Short Form-36
SNP	single nucleotide polymorphisms
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
V/F	volume of distribution
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment Questionnaire

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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 rate of 8.3 to 214 cases per 100,000 persons.[2]

CD has been characterized by significant morbidity including abdominal pain, diarrhea, weight loss/malnutrition, a progressive nature that leads to complications such as fistulas, strictures and abscesses.

Given that no known medical or surgical cure currently exists for CD, the therapeutic strategy is to reduce symptoms, improve quality of life (QoL), reduce endoscopic evidence of inflammation, and minimize short- and long-term toxicity and complications.[3] Currently, patients with moderate to severe disease who have failed aminosalicylates or topical treatments are usually treated with conventional pharmacologic interventions, which include corticosteroids and immunosuppressive agents such as azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX).[1,4] Local or systemic corticosteroids may be used for induction of remission, but are not recommended as maintenance therapy, due to their side effect profile.[5,6] Immunosuppressants are recommended for use as maintenance therapy; however, not all patients have a clinically meaningful response or a sustained response to these therapies. Patients who do not respond to conventional therapies may be treated with biologics, such as anti-tumor necrosis factor (TNF) α therapies.[1,4] However, approximately 40% of patients do not respond to their first biologic therapy (primary non-responders).[7-11] 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).[8,10] 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 or other biologic therapies.[10,12] Vedolizumab, an anti-integrin biologic, is associated with a relatively slower onset of action and the majority of subjects in the Phase 3 clinical induction (85%) and maintenance (68.6%) trials did not achieve remission. Furthermore, vedolizumab treatment has not been associated with reduction of systemic signs of inflammation (such as C-reactive protein [CRP]).[13] More recently, ustekinumab, which targets the p40 subunit shared by interleukin (IL)-23 and IL-12, demonstrated efficacy in three Phase 3 studies (UNITI-1, UNITI-2,[14] and IM-UNITI[15]) in subjects with CD. In UNITI-1 and UNITI-2, clinical remission rates at Week 8 were 20.9% and 40.2%, respectively, compared with placebo (7.3% and 19.6%, respectively). After maintenance treatment, 53.1% of patients receiving ustekinumab achieved clinical remission, versus 35.9% of patients receiving placebo at Week 44. The available treatment options may also be associated with some adverse events (AEs) that may limit the use or require close monitoring. Therefore, there remains a medical need for additional therapeutic options in CD for patients with inadequate response to or intolerance to conventional therapies and anti-TNF α agents.

Rationale for Development of a JAK Inhibitor in CD

Inhibition of Janus kinase (JAK)-mediated pathways is a promising approach for the treatment of patients with CD.[16] The JAK family is composed of 4 family members: JAK1, 2, 3, and Tyrosine kinase 2. These cytoplasmic kinases are associated with membrane cytokine receptors such as common gamma-chain (CGC) receptors and the glycoprotein 130 (gp130) transmembrane proteins.[17] Activation of JAK pathways 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.[18]

In CD, the imbalance between anti-inflammatory and pro-inflammatory cytokines in the mucosal immune system is thought to play an important role. Cells from the innate

mucosal immune system, i.e., TH1 or TH17, are over-activated and secrete various pro-inflammatory cytokines such as interferon gamma (INF-g), TNFα, IL-6, IL-1b, IL-12, IL-23. These cytokines signal via JAK pathways.[19]

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.[20] Cytokines such as IL-6 bind to gp130 and transduce its signal predominantly via JAK1.[21] 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.[22] 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.

Tofacitinib, a pan-JAK inhibitor approved for use in rheumatoid arthritis (RA), failed to demonstrate the efficacy in two Phase 2 studies in CD.[23] Filgotinib, a second generation JAK inhibitor, selective for JAK1, induced clinical remission in significantly more patients with active CD compared with placebo, however, did not demonstrate endoscopic improvement after a 10-week induction period.[24]

JAK inhibitors have been associated with infections, including herpes zoster reactivation, malignancies, and asymptomatic, mild and reversible changes in levels of hemoglobin, lymphocyte counts, white blood cell (WBC) counts, serum creatinine, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and liver transaminases (alanine transaminase [ALT], aspartate transaminase [AST]) and creatine phosphokinase (CPK).[24,25]

Upadacitinib is a novel selective JAK1 inhibitor being developed for the treatment of adult patients with CD. In an in vitro setting, upadacitinib potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit-risk profile in patients with CD. The clinical hypothesis is that upadacitinib should be effective in decreasing inflammation and damage associated with CD by interfering with JAK1-mediated signaling pathways (i.e., IL-6) without causing excessive anemia due to its

reduced activity against JAK2 (half maximal inhibitory concentration [IC_{50}] 120 nM), which is essential for erythropoietin signaling. Upadacitinib is also less potent against JAK3 (IC_{50} 2.3 µM), an important component of lymphocyte activation and function. As such, treatment with upadacitinib, a selective JAK1 inhibitor with reduced JAK3 inhibition, could result in a decreased risk for infection (including viral reactivation) and/or malignancy compared to less selective JAK inhibitors.

Additional information regarding the preclinical toxicology, metabolism, pharmacology, safety experience and indications under study with upadacitinib can be found in the current edition of the Investigator's Brochure.[26]

Upadacitinib has been evaluated in Phase 2 dose ranging placebo-controlled studies in subjects with moderately to severely active CD (Study M13-740; NCT02365649) and moderately to severely active RA (Study M13-537; NCT02066389 and Study M13-550; NCT01960855). The 52-week data in subjects with CD from Study M13-740 suggest that upadacitinib may alleviate signs and symptoms of active CD and reduce mucosal inflammation.

In Study M13-740, 220 subjects were randomized to 4 twice daily (BID), 1 once daily (QD) dose regimens of upadacitinib immediate release capsules (3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID, and 24 mg QD), or to placebo. As induction treatment, a statistically significant dose-response relationship was observed with upadacitinib for the co-primary endpoint of endoscopic remission. A dose-response was not observed for the clinical remission co-primary endpoint; however, a new endpoint for potential use as primary in Phase 3 demonstrated a statistically significant dose-response relationship for clinical remission in the 6 mg BID and 24 mg BID dose groups compared to placebo. Endoscopic response was statistically significantly better in all upadacitinib dose groups except for 3 mg BID compared to placebo. In the Extension Phase, subjects who achieved response and were re-randomized to the 12 mg BID group achieved statistically significant clinical remission and endoscopic outcomes compared to subjects in the 3 mg BID group at Week 52.

Safety data from the induction portion of Study M13-740 were consistent with the profile observed in the Phase 3 RA studies. The incidences of AEs in Study M13-740 were numerically higher in the upadacitinib dose groups, with no dose relationship. Infections occurred with higher incidences in the upadacitinib groups than the placebo group, but also did not show dose-related increases. The most frequently reported AEs (≥ 5%) in the upadacitinib treated subjects were headache, Crohn's disease, abdominal pain, fatigue, nasopharyngitis, urinary tract infection, upper respiratory tract infection, vomiting and pyrexia. Upadacitinib continued to be generally well tolerated following re-randomization of subjects at Week 16 to upadacitinib 3 mg BID, 6 mg BID, 12 mg BID, or 24 mg QD through Week 52 of the Extension Phase. There were 5 subjects with non-serious events of herpes zoster reactivation. Two events of gastrointestinal perforation were reported in 2 subjects; 1 subject had worsening of CD and associated fistulization and abscess, and the other subject had a perforation in an area of fissuring ulcer. Similar to the RA Phase 3 studies, increase in LDL-C and HDL-C, reductions in natural killer (NK) cells, slight decreases in red blood cell (RBC) counts, and asymptomatic and transient CPK elevations were observed. No deaths were reported during the study.

All subjects who complete Study M13-740 are eligible to enroll in Study M14-327, a Phase 2, open-label extension study to evaluate the long-term safety and efficacy of upadacitinib.

Study M14-431 will evaluate one induction dose of upadacitinib (45 mg QD) of the once-daily modified-release tablet formulation. The selection of this dose was informed by the analysis of the 16-week safety, efficacy, and exposure-response Phase 2 data from Study M13-740. In addition, all the currently available pharmacokinetic (PK), pharmacodynamic, safety, and efficacy data from upadacitinib studies were used to support the selection of this dose. Upadacitinib 45 mg QD, dosed for up to 12 weeks, is expected to be efficacious with an acceptable safety profile, and upadacitinib 15 mg QD and 30 mg QD, dosed for up to 240 weeks as maintenance treatment, are expected to be efficacious with acceptable safety profiles.

In this study, subjects with moderately to severely active CD will be enrolled. Moderate to severe active disease will be determined by evidence of active intestinal mucosal inflammation assessed by the Simplified Endoscopic Score for CD (SES-CD), confirmed by a central endoscopy reader; and the presence of signs and symptoms of the patient-reported outcomes and Crohn's Disease Activity Index (CDAI) subcomponents of very soft/liquid stool frequency and abdominal pain. This is supported by post-hoc analyses of the adalimumab studies, the Phase 2 risankizumab Study 1311.6 and upadacitinib Study M13-740, where the proposed inclusion criterion of very soft/liquid stool frequency and abdominal pain score was met by 85% to 92% of subjects with baseline CDAI 220 to 450, respectively.

3.1 Differences Statement

This study is designed to evaluate the efficacy and safety of upadacitinib 45 mg QD versus placebo in subjects with moderately to severely active CD. The primary difference between Study M14-431 and the prior Phase 2 study of upadacitinib in CD is that this study will test a QD oral formulation of upadacitinib and confirm the efficacy of upadacitinib in a larger CD population with inadequate response or intolerance to biologic therapies. Additionally, some efficacy endpoint definitions in this study are different from Phase 2 to reflect the changing regulatory requirements for pivotal registrational studies for new agents for the treatment of CD.

3.2 Benefits and Risks

Although conventional and newer treatments such as biologic therapies have improved the standard of care for patients with CD, there remains a significant unmet medical need for patients with inadequate or loss of response to these agents, and efforts are ongoing to develop novel therapies.

Clinical efficacy in targeting pro-inflammatory cytokines and downstream signaling pathways has been demonstrated in CD with second generation JAK inhibitors, including upadacitinib. These drugs are also being studied for the treatment of patients with ulcerative colitis.

Upadacitinib 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 pan-JAK inhibition, which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.

Adverse events (AEs) such as infections, herpes zoster reactivation, malignancies, and hematologic AEs have been observed with JAK inhibition. By its selectivity for JAK1, upadacitinib may be able to decrease inflammation mediated by JAK1 signaling while having less inhibitory effect on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with less selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.

The available long-term safety data from the Phase 3 rheumatoid arthritis (RA) studies with upadacitinib did not show any new significant safety concerns compared to the marketed JAK inhibitors. The findings of an increased risk of infections, herpes zoster, and abnormal laboratory changes have been observed (e.g., elevations of serum transaminases, lipids, creatine phosphokinase, and reductions in hemoglobin and white blood cells) with upadacitinib therapy. The incidence rates of other clinically important adverse events such as cardiovascular events, malignancies and mortality reported during the RA studies were within the expected range for the general population or for a population of patients with moderately to severely active RA. Events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including upadacitinib. In addition, no new safety signals have been identified in the Phase 2 (Study M13-740; NCT02365649) study of moderately to severely active CD with upadacitinib during 52 weeks of treatment.

The results of genetic toxicology testing indicate that upadacitinib is not genotoxic; however, upadacitinib is teratogenic based on animal studies, which necessitates avoidance of pregnancy in females of childbearing potential. Based on the calculated safety margins for human fetal exposure with seminal fluid transfer, there is judged to be no risk to the pregnancy of female partners of male subjects who are treated with upadacitinib.

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.

Taken together, the safety and efficacy data from upadacitinib studies to date show a favorable benefit:risk profile for upadacitinib and support the continued investigation of upadacitinib in patients with various autoimmune/inflammatory conditions.

AbbVie is conducting a Phase 3 study in subjects with CD based on the following supportive findings: 1) demonstrated clinical and endoscopic improvements in the induction treatment in a Phase 2 dose-ranging study; and 2) safety results were consistent with those known to be associated with JAK inhibition. The current Phase 3 Study M14-431 will further evaluate the benefit to risk profile of upadacitinib in CD subjects who have inadequately responded to, or are intolerant to, biologic therapies.

In view of the coronavirus (COVID-19) pandemic, the benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

4.0 Study Objective

The objective of Study M14-431 is to evaluate the efficacy and safety of upadacitinib compared to placebo as induction therapy in subjects with moderately and severely active CD.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

Study M14-431 is a Phase 3, randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib, an orally administered JAK1 inhibitor in adult subjects with moderately to severely active CD who have inadequately responded to or are intolerant to biologic therapy. The study will allow enrollment of up

to 35% of subjects who have demonstrated inadequate response or intolerance to 3 or more biologics.

The study will enroll approximately 625 subjects at approximately 400 study centers worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

This study will evaluate one induction dose of upadacitinib (45 mg QD) (Figure 1).

Subjects who consent and meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into this study which encompasses three parts:

- **Part 1:** a randomized, double-blind, placebo-controlled induction period,
- **Part 2:** an open-label, single-arm active induction period, and
- **Part 3:** an Extended Treatment Period for non-responders from Part 1 or Part 2.

Part 1

In Part 1, subjects (n = 495) will be randomized in a 2:1 ratio to upadacitinib 45 mg QD or matching placebo for 12 weeks (Figure 1). The randomization will be stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologic treatments (> 1 and ≤ 1). The data collected from subjects from Part 1 will be used for the primary efficacy analysis.

Visits during the study will occur at Baseline and Weeks 2, 4, 8, and 12/Premature Discontinuation (PD) to collect clinical, endoscopic and laboratory assessments of disease activity.

At Week 12, subjects achieving clinical response, defined as ≥ 30% decrease in average daily very soft or liquid stool frequency (SF) and/or ≥ 30% decrease in average daily abdominal pain (AP) score (both not worse than Baseline) may be eligible to enter the 52-week, double-blind, maintenance portion of Study M14-430.

All subjects who do not achieve clinical response at Week 12 will be able to enroll in Part 3 (Extended Treatment Period) and receive double-blind upadacitinib until Week 24/PD.

Subjects are not eligible to enter Study M14-430 until the ileocolonoscopy procedure at Week 12 has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, a subject can enroll in Study M14-430 if clinical response was achieved at Week 12.

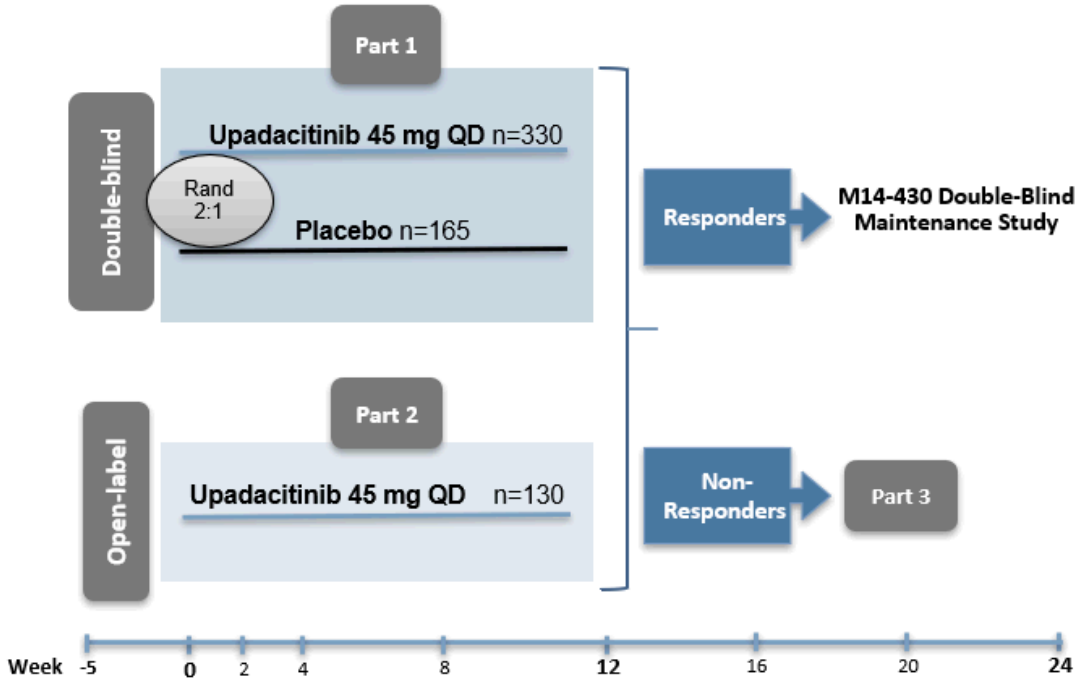
Part 2

Part 2 is an open-label portion (open-label cohort) of this study. Once enrollment in Part 1 is complete, approximately 130 subjects will be enrolled in Part 2 to receive upadacitinib 45 mg QD for 12 weeks (Figure 1). The objective of Part 2 is to have a sufficient number of subjects with clinical response to be re-randomized in the double-blind maintenance portion of Study M14-430, while minimizing unnecessary exposure to placebo. The data collected from subjects from Part 2 will not be part of the primary efficacy analysis for this study, will use descriptive statistics, and will be reported separately in the clinical study report.

Visits during the study will occur at Baseline and Weeks 2, 4, 8, and 12/PD to collect clinical, endoscopic and laboratory assessments of disease activity.

At Week 12, subjects achieving clinical response may be eligible to enter Study M14-430 (Figure 1). Subjects who do not achieve clinical response at Week 12 will be able to participate in Part 3 (Extended Treatment Period) to receive open-label upadacitinib 30 mg QD until Week 24/PD.

Figure 1. Study M14-431 Study Design – Part 1 and Part 2



QD = once daily; Rand = randomization

The study will allow the enrollment of up to 10% of subjects who received a JAK inhibitor prior to study entry if they have not had inadequate response or loss of response.

Part 3

Part 3 is a 12-week Extended Treatment Period consisting of 3 cohorts for subjects who do not achieve clinical response at Week 12 in Part 1 or Part 2 (Figure 2). The objectives of Part 3 are to offer blinded upadacitinib induction treatment to placebo non-responders from Part 1 and to evaluate delayed clinical response to upadacitinib in subjects who did not initially respond to upadacitinib during Part 1 or Part 2.

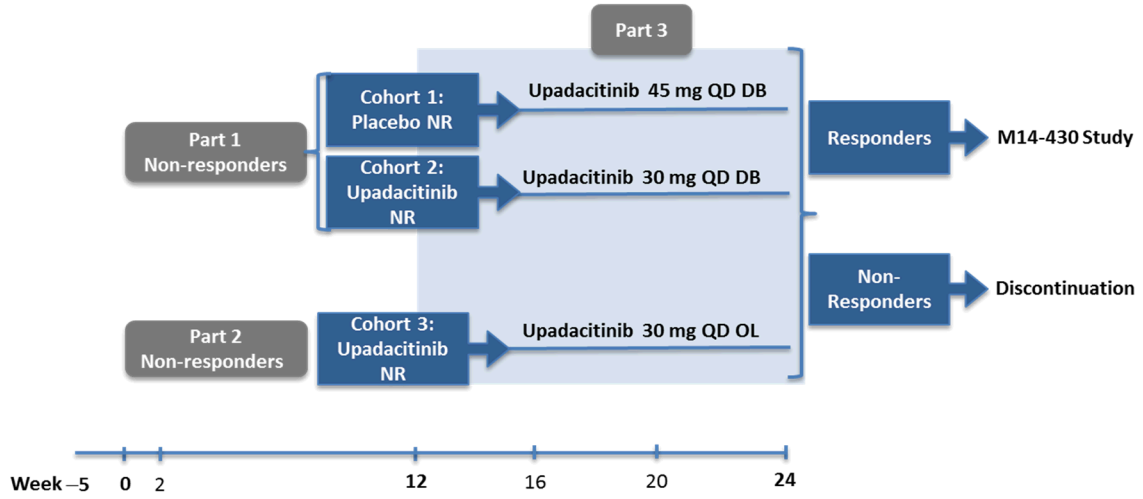
- **Cohort 1:** Subjects who received placebo in Part 1 and did not achieve clinical response at Week 12 are eligible to receive double-blind induction treatment with upadacitinib 45 mg QD for 12 weeks (until Week 24).
- **Cohort 2:** Subjects who received double-blind upadacitinib in Part 1 and did not achieve clinical response at Week 12 are eligible to receive double-blind upadacitinib 30 mg QD for 12 weeks (until Week 24).
- **Cohort 3:** Subjects who received open-label upadacitinib during Part 2 and did not achieve clinical response at Week 12 are eligible to receive open-label upadacitinib 30 mg QD for 12 weeks (until Week 24).

Subjects in Cohort 1 and 2 will remain blinded to treatment to avoid unmasking the treatment received during Part 1. The data collected from subjects from Part 3 will not be part of the primary efficacy analysis, will use descriptive statistics, and will be reported separately in the clinical study report.

Subjects are not eligible to enter in Part 3 until the Week 12 endoscopy has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, a subject can continue into Part 3. Visits will occur at Weeks 16, 20 and 24/PD to collect clinical, endoscopic and laboratory assessments of disease activity.

During Part 3, subjects with persistent symptoms or worsening of CD may be discontinued at any time.

Figure 2. Study M14-431 Study Design – Part 3



DB = double-blind; NR = non-responders; OL = open-label; QD = once daily

At Week 24, subjects who achieve clinical response may be eligible to enter Study M14-430. Subjects are not eligible to enter Study M14-430 until the ileocolonoscopy procedure at Week 24 for evaluation of mucosal inflammation has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, a subject can enroll if clinical response was achieved at Week 24.

Subjects who do not achieve clinical response at Week 24 will be discontinued from Study M14-431 and will receive standard of care treatment at the investigator's discretion. Subjects who do not achieve clinical response at Week 24 and all subjects who prematurely discontinue the study will have a follow-up visit 30 days from the last dose of study drug to collect information on new or ongoing AEs and laboratory assessments. Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the investigator.

The duration of the study could be up to 33 weeks, including Screening Period (5 weeks), a 12-week double-blind or open-label cohort Induction Period (Part 1 or Part 2), a

12-week Extended Treatment Period (Part 3), and a 30-day follow-up for subjects who do not enroll into Study M14-430.

At the Screening Visit, all subjects will be provided with an electronic diary. Subjects will be instructed and trained on how to record CD-related symptoms (including total and very soft and liquid number of stools and abdominal pain), general well-being and use of anti-diarrheals on a daily basis; and use of medications for endoscopy preparation throughout the study. The very soft and liquid stools are defined as consistency Type 6 or Type 7 based on the Bristol Stool Chart (Appendix F).

The diary will be reviewed by site personnel with the subject at each visit and for the assessment of the clinical endpoints. At each Study Visit, routine physical examination including evaluation of vital signs, extra-intestinal manifestations (EIMs), presence or absence of fistulas; calculation of CDAI score, total and average daily very soft or liquid SF and average daily AP (very soft or liquid SF and AP entries from the most recent 7-day period prior to each study visit will be used); monitoring of AEs; concomitant medications and laboratory assessments will be performed. The very soft or liquid SF and AP score values represent the unweighted daily averages of the corresponding subscores from the CDAI. Additionally, subjects will complete QoL, CD symptoms, symptoms impact on QoL, and work productivity questionnaires throughout the study as indicated in Appendix C.

Clinical samples for urinalysis, chemistry and hematology, high sensitivity C-reactive protein (hs-CRP), plasma upadacitinib concentrations will be collected. In addition, stool samples for calprotectin analysis will be collected and should be taken before starting bowel preparations for endoscopy.

Subjects will undergo a full colonoscopy (ileocolonoscopy) for evaluation of mucosal inflammation using the SES-CD. All endoscopies will be centrally read to document eligibility at Screening, and for Week 12 and 24/PD assessments. Biopsy to confirm diagnosis (during Screening) or to rule out dysplasia/malignancy may be performed

during the same time points as the endoscopy. Optional exploratory research samples may be taken during the study (see also Appendix C).

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 then undergo the screening procedures outlined in Appendix C. Laboratory values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

The length of time between Screening and the Baseline visit must allow time for endoscopy central reading and review of laboratory results. The Screening period will be a minimum of 8 days.

Subjects who have been taking exclusionary medications prior to Screening or Baseline must complete the medication(s) washout within the duration described in the protocol Exclusion Criteria Section 5.2.2 prior to the Baseline Visit (i.e., 8-week washout of a biologic therapy). During Screening, biologic drug levels may be optionally assessed at the investigator's discretion as an alternative to completing the required washout period: (1) infliximab and natalizumab: may be tested approximately 4 weeks from the last dose; (2) adalimumab, certolizumab, golimumab, or vedolizumab: may be tested approximately 6 weeks from the last dose; (3) ustekinumab: may be tested approximately 8 weeks from the last dose. If the biologic drug is not detected, the subject will be considered as eligible and the washout period is not required.

All subjects need to have their average daily very soft or liquid SF and average daily AP score calculated and meeting eligibility criteria before randomization at Baseline.

Re-Screen

Subjects who initially screen fail for the study are permitted to re-screen once following re-consent. For additional re-screenings, AbbVie Therapeutic Area Medical Director (TA MD) approval is required. Laboratory values can be re-tested once during the re-screening period. As appropriate, sites are encouraged to contact the AbbVie TA MD to confirm if subjects should or should not be re-screened. All screening procedures with the possible exceptions noted below will be repeated during re-screening. The subject must meet all of the inclusion criteria 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. The re-screening period will be a minimum of 8 days, with the exception of subjects who are re-screened immediately after being screen failed and do not require a repeated endoscopy. The minimum re-screening period for these subjects will be 4 days.

If the subject had a complete initial screening evaluation including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB [tuberculosis] Gold In Tube test) and/or a purified protein derivative (PPD) test (or equivalent) (or both if required per local guidelines), chest x-ray and electrocardiogram (ECG), tests for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and beta-D-glucan (Japan only), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met, there are no changes in the subject's medical history that would warrant re-testing, and no more than 90 days have passed since the collection date of the assessment. If a subject is being re-screened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry, hematology, urinalysis, serum pregnancy, and *Clostridium difficile* provided that the subject's health status has not changed to warrant a repeat test.

An endoscopy will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 45 days have passed between the previous screening endoscopy and Baseline.

All subjects need to have their average daily very soft or liquid SF and average daily AP score calculated and meeting eligibility criteria before randomization at Baseline.

12-Week Induction Period – Part 1 and Part 2

This period will begin at the Baseline Visit and will end at the Week 12 Visit. At the Baseline Visit, subjects who meet all of 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. In Part 1, subjects will be randomized to a double-blind induction period. In Part 2, subjects enrolled will receive open-label upadacitinib. During this induction period, all subjects will visit the study site at Weeks 2, 4, 8, and 12/PD, and a ± 3-day window is permitted around scheduled study visits. The last dose of study drug during this period is taken the day prior to the Week 12 visit.

12-Week Extended Treatment Period – Part 3

This period will begin at Week 12 and will end at the Week 24 Visit. At Week 12, subjects who do not achieve clinical response will enter Part 3. Clinical response is defined as ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP and both not greater than Baseline. During this period, all subjects will visit the study site at Weeks 16, 20, and 24/PD. A ± 3-day window is permitted around scheduled study visits. The last dose of study drug during this period is taken the day prior to the Week 24 visit.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time (refer to Section 5.4.1 for additional details). If a subject prematurely discontinues study drug treatment and study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, if the subject is willing, a 30-day follow-up visit (or telephone call if a visit is not possible) should occur to determine the occurrence or status of any new or ongoing AEs/serious

adverse events (SAEs). Subjects who discontinue the study prematurely after randomization will not be replaced.

Discontinuation of Study Drug and Continuation of Study Participation

Subjects may discontinue study drug treatment but may choose to continue to participate in the study (refer to Section 5.4.1 for additional details). Subjects who prematurely discontinue study drug should complete a PD visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix C, and adhere to all study procedures except for dispensing study drug and PK sample collection, and blood, stool and biopsy sample collection for optional exploratory research. As the subject has discontinued study drug, all rescue and efficacy driven discontinuation criteria no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

Unscheduled Visits

Unscheduled Visits may occur when the subject is coming in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood samples will be obtained for the laboratory tests listed in Table 2 or for other tests at the investigator's discretion. 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.

Follow-Up Visit

A follow-up visit will occur approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AE/SAEs and laboratory assessments.

Subjects will complete the follow-up visit when they have either

- Completed the final study visit and have not enrolled in Study M14-430 OR

- Prematurely discontinued study drug and study participation.

The follow-up visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least one study visit at least 30 days after last study visit.

If a follow-up visit is not possible, a telephone call may be possible to collect information about new or ongoing AEs.

Study visits may be impacted due to the COVID-19 pandemic or any state of emergency or pandemic situation. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others may be performed. Additional details are provided in the subsequent sections. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

5.2 Selection of Study Population

It is anticipated that approximately 625 subjects with active moderately to severely active CD will be enrolled at approximately 400 sites worldwide.

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

5.2.1 Inclusion Criteria

1. Male or female aged ≥ 18 and ≤ 75 years of age or minimum age of adult consent according to local regulations at Baseline.
2. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, as determined by the investigator, must be available.

3. SES-CD (excluding the presence of narrowing component) ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), as confirmed by a central reader.
4. Average daily very soft or liquid SF ≥ 4.0 **AND/OR** average daily AP score ≥ 2.0 at Baseline.
5. Demonstrated an inadequate response or intolerance to one or more of the following biologic agents as defined by:
   - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at Baseline and Weeks 2 and 6),
   - At least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous [SC] dose at Baseline, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Baseline, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),
   - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Baseline, and Weeks 2, and 4),
   - At least one 6-week induction regimen of vedolizumab (300 mg IV at Baseline and Weeks 2, and 6),
   - At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8],
   - Recurrence of symptoms during scheduled maintenance dosing following prior clinical response to the above biologics,
   - Intolerance to a biologic may include, but not limited to infusion-related reaction, rash, serum sickness, anaphylaxis, elevated liver enzymes, demyelination, congestive heart failure, infection. Demonstration of intolerance requires no minimum dose or duration of use.
6. Women of childbearing potential (refer to Section 5.2.4), must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing.

   Note: subjects with borderline serum pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological cause of a

borderline result and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

7. 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 Baseline Visit through at least 30 days after the last dose of study drug.
8. Subject is judged to be in good health as determined by the principal investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead ECG performed during Screening.
9. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and comply with the requirements of this study protocol. In countries where the subject is 18 years-old but not of minimum adult age to consent according to local regulations, a subject's parent or guardian must be willing to provide written informed consent (e.g., Japan < 20 years old).

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

Concomitant Medications and Treatments

2. Subject on CD-related antibiotics who:
   - has not been on stable doses of these medications for at least 14 days prior to Baseline, or

- has discontinued these medications within 14 days of Baseline.

3. Subject on oral aminosalicylates who:
   - has not been on stable doses of these medications for at least 14 days prior to Baseline, or
   - has discontinued these medications within 14 days of Baseline.
4. Subject on corticosteroids who meet the following:
   - prednisone or equivalent dose > 30 mg/day; or
   - budesonide > 9 mg/day; or
   - has not been on the current course for at least 14 days prior to Baseline and on a stable dose for at least 7 days prior to Baseline.
5. Subject on MTX who:
   - has not been on the current course for ≥ 42 days prior to Baseline, and
   - has not been on a stable dose for ≥ 28 days prior to Baseline

Medications and Treatments During the Screening Period

6. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral/intramuscular (IM) anti-infectives within 14 days prior to the Baseline Visit.
7. Subject requiring or receiving any parenteral nutrition and/or exclusive enteral nutrition.
8. Subject who received oral or parenteral traditional Chinese medicines within 30 days prior to Baseline.
9. Subject who received any live vaccination within 30 days (or longer if required locally [e.g., 8 weeks for Japan]) prior to Baseline, or who is expected to need live vaccination during study participation including at least 30 days (longer if required locally [e.g, 8 weeks for Japan]) after the last dose of study drug.

10. Subject who received cyclosporine, tacrolimus, mycophenolate mofetil, or thalidomide within 30 days prior to Baseline.
11. Subject who received azathioprine (AZA) or 6-mercaptopurine (6-MP) within 10 days of Baseline.
12. Subject who received fecal microbial transplantation within 30 days prior to Baseline.
13. Subject who received nonsteroidal anti-inflammatory drugs (NSAIDs) within 7 days prior to Baseline, except topical NSAIDs and low dose aspirin for cardiovascular protection.
14. Systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to Table 1 for examples of commonly used strong CYP3A inhibitors and inducers).

Prior Medications and Treatments

15. Subject who received any of the following agents:
    - adalimumab, certolizumab, golimumab, infliximab, natalizumab, vedolizumab within 8 weeks prior to Baseline; or
    - ustekinumab within 12 weeks prior to Baseline.
        - Note: If there is proper documentation of an undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.
    - any investigational agent within 30 days or 5 half-lives prior to Baseline, whichever is longer, or is currently enrolled in another interventional study.
16. Subject with previous exposure to a JAK inhibitor (e.g., tofacitinib, baricitinib, filgotinib) within 30 days from Baseline.

    Note: Subjects who received a JAK inhibitor prior to study entry may be enrolled if they have not had inadequate response or loss of response.

17. Subject has been taking both oral budesonide (or oral beclomethasone) and oral prednisone (or equivalent) simultaneously, with the exception of topical or inhalers within 14 days prior to Screening or during the Screening Period.
18. Subject received IV corticosteroids within 14 days prior to Screening or during the Screening Period.
19. Subject has received therapeutic enema or suppository (i.e., rectal aminosalicylates/corticosteroids), other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening period.
20. Subject who received apheresis (e.g., Adacolumn apheresis) within 60 days prior to Screening or during the Screening Period.
21. Subject has cannabis use, either recreational or for medical reasons, within 14 days prior to Baseline or any history of clinically significant (per investigator's judgment) drug or alcohol abuse in the last 6 months.
22. Subject who previously received stem cell transplantation (except for local stem cell therapy for complex perianal fistula).
23. Subject has been a previous recipient of an organ transplant which requires continued immunosuppression.

CD Related

24. Subject with the following ongoing known complications of CD:
    - abscess (abdominal or peri-anal),
    - symptomatic bowel strictures,
    - > 2 entire missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum,
    - fulminant colitis,
    - toxic megacolon,

- or any other manifestation that might require surgery while enrolled in the study.

25. Subject with ostomy or ileoanal pouch.

26. Subject diagnosed with conditions that could interfere with drug absorption including but not limited to short gut or short bowel syndrome.

27. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of > 3 bowel resections.

Safety

28. Subject with positive *Clostridium difficile (C. difficile)* toxin stool assay during Screening.

29. Any active, chronic or recurrent infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or HIV infection. Active HBV, HCV and HIV are defined as:

    - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV-deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects;
    - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab);
    - HIV: confirmed positive anti-HIV antibody (HIV Ab) test;
    - Confirmed COVID-19: the Baseline visit must be at least 14 days from onset of signs/symptoms or positive SARS-CoV-2 test, symptomatic subjects must have recovered, defined as resolution of fever without use of anti-pyretics and improvement in symptoms;
    - Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high risk behavior should undergo molecular

(e.g., PCR) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure.

30. Subject has active TB or meets TB exclusionary parameters (refer to Section 5.3.1.1 for specific requirements for TB testing).

31. History of any malignancy except for successfully treated nonmelanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.

32. Prior or current gastrointestinal dysplasia, other than completely removed low-grade dysplastic lesions in any biopsy performed during or before the Screening endoscopy.

33. History of gastrointestinal perforation (other than appendicitis or mechanical injury), diverticulitis or significantly increased risk for gastrointestinal perforation per investigator judgment.

34. Female who is pregnant, breastfeeding, or is considering becoming pregnant during the study or within 30 days after the last dose of study drug.

35. History of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same.

36. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:

- Serum AST or ALT > 2.0 × upper limit of normal (ULN);
- Total WBC count < 2500/µL;
- Estimated glomerular filtration (eGFR) rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 mL/min/1.73 m^2;
- Hemoglobin < 9g/dL;
- Platelet count < 100,000/µL;
- Absolute neutrophil count (ANC) < 1200/µL;
- Absolute lymphocyte count (ALC) < 750/µL.

37. Any of the following cardiovascular conditions or thrombotic conditions:

- recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
- current uncontrolled hypertension as defined by a confirmed systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg;
- prior history of thrombotic events including deep venous thrombosis and pulmonary embolism;
- known inherited conditions that predispose to hypercoagulability.

38. History of clinically significant medical conditions or any other reason that in the opinion of the investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.

39. For Japan subjects only: positive result of beta-D-glucan or 2 consecutive indeterminate results of beta-D-glucan during the Screening Period.

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 is receiving at the time of screening, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF).

If subjects have/had ever been treated with CD-related, including, but not limited to corticosteroid, immunosuppressants (AZA, 6-MP or MTX), aminosalicylates, CD-related antibiotics or biologic agents, 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.

The AbbVie TA MD identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.2 Concomitant Therapy

Changes in all concomitant medications will be assessed at each study visit from Baseline through Week 12/PD and during Weeks 12 to 24/PD visits for subjects who participate in the Part 3. Any changes will be documented in the source documents and captured on the appropriate eCRF page.

5.2.3.2.1 Concomitant CD-Related Medications (Antibiotics, Aminosalicylates, and/or Methotrexate)

All subjects receiving a stable dose of CD-related antibiotics, aminosalicylates, or MTX at Baseline should maintain their concomitant treatments, without dose changes through the end of the study. Initiating and/or changing doses of these medications are prohibited during the study. Doses of CD-related antibiotics, aminosalicylates, or MTX may be decreased in the event of moderate-to-severe treatment related toxicities.

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

5.2.3.2.2 Concomitant Corticosteroids

Subjects who enter the study on oral corticosteroids are not allowed to change the corticosteroid dose during the first 4 weeks of the induction treatment period. Doses of corticosteroids may be decreased during the first 4 weeks only in the event of moderate-to-severe treatment related toxicities. At Week 4, subjects should have their corticosteroid dose reduced according to a tapering schedule described in Section 5.3.1.1 Study Procedures.

Subjects who do not achieve clinical response at Week 12 in Part 1 or Part 2, and enter Part 3 without having completed the steroid taper should resume the corticosteroid taper at Week 16, according to the tapering schedule.

Initiating locally acting (rectal or suppository) or systemic corticosteroids for any reason is prohibited during the induction treatment period and will be considered a protocol deviation and must be discussed with the TA MD.

Use of inhaled or topical (except rectal or suppository) corticosteroids is not restricted.

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

5.2.3.3 Prohibited Therapy

Biologic Therapies

Subjects must have discontinued any biologic therapy prior to the first dose of study drug as specified in the washout procedures in Exclusion Criterion 15, Section 5.2.2. For all other biologic therapies, contact the AbbVie TA MD for the washout period required prior to the first dose of study drug.

Therapies including but not limited to the following biologic therapies are prohibited medications during the study:

- Adalimumab
- Etanercept
- Infliximab
- Abatacept
- Anakinra
- Rituximab
- Natalizumab
- Tocilizumab
- Golimumab
- Certolizumab
- Ustekinumab
- Belimumab

- Secukinumab
- Vedolizumab

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study. The most common strong CYP3A inhibitors and inducers are listed in Table 1.

Table 1. Examples of Commonly Used Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir	Avasimibe
Cobicistat	Carbamazepine
Clarithromycin	Phenytoin
Conivaptan	Rifampin (rifampicin)
Grapefruit (fruit or juice)	Rifapentine
Indinavir	St. John's Wort
Itraconazole	
Ketoconazole	
Lopinavir/Ritonavir	
Mibefradil	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Troleandomycin	
Voriconazole	

CYP = cytochrome P450

Traditional Chinese Medicine

Oral and parenteral traditional Chinese medicine is not permitted during the study, and subjects must have discontinued traditional Chinese medicine at least 30 days prior to the first dose of study drug.

Investigational Drugs

Subjects who have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in this study. Investigational drugs are also prohibited during the study.

Vaccines

Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, tetanus-diphtheria-acellular pertussis (Tdap), and herpes zoster (Shingrix, non-live, recombinant). If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) at least 30 days (or longer, if required locally [e.g., or 8 weeks in Japan]) before first dose of study drug with appropriate precautions and are not allowed during study participation including at least 30 days (or longer, if required locally) after last dose of oral study drug. Live vaccines are NOT allowed during the study. If the herpes zoster live attenuated vaccine (Zostavax) is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing immunity to varicella should be confirmed with antibody testing at or prior to screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative the herpes zoster vaccine should not be administered.

Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Zostavax (herpes zoster, live attenuated);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;

- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid (oral)

Other medications prohibited during the study:

- JAK inhibitors (e.g., tofacitinib [Xeljanz®])
- Cyclosporine, tacrolimus, thalidomide, mycophenolate mofetil, AZA, or 6-MP.
- NSAIDs (except topical NSAIDs and the use of low dose aspirin for cardiovascular protection).
- Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy.
- Any parenteral nutrition and exclusive enteral nutrition.
- Cytapheresis treatment (granulocytapheresis, etc.) (in Japan and China only).
- Cannabis.

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

5.2.4 Contraception 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 a follicle-stimulating hormone (FSH) level > 40 mIU/mL.

If the female subject is ≤ 55 years of age AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.

- If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol-specified contraception is required.
- If the FSH is tested and the result is consistent with postmenopausal status, contraception is not required.
- If the FSH is tested and the result is consistent with premenopausal status, contraception is required, and pregnancy testing requirements for females of childbearing potential must be followed (see Section 5.3.1.1, pregnancy test).

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control (for subjects in the US and where appropriate per local requirements: must simultaneously use two of the following highly effective methods of birth control; or one of the following highly effective methods of birth control PLUS a barrier [condoms, diaphragm or cervical cap] with spermicide) that is effective from Study Day 1 (Baseline) (or earlier) through at least 30 days after the last dose of study drug:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, and injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1 (Baseline).
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Day 1 (Baseline).
- Bilateral tubal occlusion/ligation.

- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success and is the sole sexual partner.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- True abstinence (if acceptable per local requirements): defined as 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).
    - In the US, true abstinence applies only to women of childbearing potential who do not have male partners and are not engaging in heterosexual intercourse as their preferred and usual lifestyle (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, progesterone-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action (initiated at least 1 month prior to Baseline), 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).

If during the course of the study a woman becomes surgically sterile or postmenopausal and complete documentation is available, contraceptive measures as defined above are no longer required.

Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.

It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Exploratory Research, 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

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C are discussed in detail in this section, with the exception of optional exploratory research (discussed in Section 5.3.1.2), drug concentration measurements (discussed in Section 5.3.2), the collection of prior and concomitant medication information (discussed in Section 5.2.3), and the collection of AE information (discussed in Section 6.1.1.1). 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, IEC/IRB approved, informed consent form for the study before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Separate written consent will be required for each subject in order to participate in the optional exploratory research. The separate written consent may be part of the main consent form. Subjects can withdraw informed consent at any time.

Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Due to the COVID-19 pandemic, any state of emergency or pandemic situation, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

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 non-CD-related medical and surgical history, including history of alcohol and nicotine use, will be taken from each subject during the Screening Visit. Additionally, a list of each subject's CD-related medical and surgical history will be recorded at Screening. Information on prior aminosalicylate, corticosteroid, immunosuppressants (e.g., AZA, 6-MP, and MTX) use, biologics, CD-related antibiotics, or any other physician prescribed therapy for CD will be obtained as outlined in Section 5.2.3.1. Information for the Montreal classification for CD will be collected at Screening for all subjects.

History of herpes zoster, herpes zoster vaccination, and hepatitis B vaccination status will be recorded as part of the medical history. An updated medical history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment.

A detailed medical history with respect to TB risk factors will be documented in the study source documentation. This information will include Bacille Calmette-Guerin (BCG) vaccination, cohabitation with individuals who have had TB, and travel to, residence in, or work in TB endemic locations.

TB Testing/TB Prophylaxis

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 previous, active, or latent TB.

At screening, all subjects will be assessed for evidence of increased risk for TB by a risk factor assessment form (Appendix D) and tested for TB infection by QuantiFERON-TB Gold test (or IGRA equivalent such as T-SPOT TB test). The PPD Skin Test (also known as a TB Skin Test or Mantoux Test) should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines). The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF.

If a subject had a negative QuantiFERON-TB Gold (and/or PPD) test within 90 days prior to Screening and source 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 may be discussed with the AbbVie TA MD. The results of the TB test(s) will be retained at the site as the original source documentation.

Subjects with documentation of a prior positive result of QuantiFERON-TB Gold Test (or equivalent) or PPD may not repeat either test at Screening or during the study and should be considered positive.

TB Test

For regions that require both PPD and QuantiFERON-TB Gold testing, both will be performed. A positive TB test is defined by local guidelines (for example, in some countries, both PPD and QuantiFERON-TB Gold are performed, and if either one is positive, the TB test is considered positive).

In the absence of local guidelines defining a positive result when both PPD and QuantiFERON-TB Gold tests are performed, the TB test is considered positive if either one is positive.

If a site has the capacity to perform both PPD and QuantiFERON-TB Gold tests, and local guidelines require only one test to be performed, then the QuantiFERON-TB Gold is the preferred test. If only a PPD is placed at screening, then the PPD will be the reference TB test to be used for the remainder of the program for that subject. Similarly, if a subject enters the study with a QuantiFERON-TB Gold test alone or other IGRA (negative result), then any future TB test performed should be a QuantiFERON-TB Gold test.

If the QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD are required per local guidelines): the PPD will be performed 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 ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had a prior positive PPD test or an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and the TB Skin Test should be considered positive.

Subjects with a negative TB test and chest x-ray not suggestive of active TB or prior TB exposure may be enrolled.

If the QuantiFERON-TB Gold test is indeterminate, the site should repeat the test with another blood sample and/or perform a PPD test. If the second QuantiFERON TB Gold test is also indeterminate or positive, the subject is considered to be positive for the purpose of the study. If the second QuantiFERON-TB Gold test is negative, the subject is considered to be negative.

In cases where the Screening QuantiFERON-TB Gold test by the central laboratory is positive and the investigator considers the subject at low risk for TB (i.e., no risk factors identified using the TB risk assessment form) and has no clinical suspicion of TB, the investigator may perform a repeat QuantiFERON-TB Gold test (or IGRA equivalent) at the local laboratory or through the central laboratory (if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the subject to be negative based on his/her clinical judgment. If the repeat testing result is positive or indeterminate, the subject is considered to be positive.

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and chest x-ray. Subjects with no signs or symptoms and a chest x-ray not suggestive of active TB may be enrolled after initiation of TB prophylaxis (see below). Subjects with evidence of active TB must not be enrolled.

Subjects with history of active TB may be enrolled if it has been adequately treated with no evidence of current active TB; subjects with inadequate documentation of treatment should be cleared by a TB specialist prior to enrollment.

TB Prophylaxis

At screening, if the subject has evidence of latent TB infection (no symptoms, positive TB test and the subject has a chest x-ray not suggestive of active TB), prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). At least 6 months of prophylaxis needs to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug. If the investigator deems that it is necessary, consultation with a TB expert could be considered.

In case of a subject at low risk for TB (i.e., no risk factors identified using the TB risk assessment form), no clinical suspicion of TB, who had a negative confirmatory repeat QuantiFERON-TB Gold test result available after initiation of isoniazid, then TB prophylaxis can be stopped.

Note: Rifampicin or rifapentine are not allowed for TB prophylaxis.

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

For subjects with completion of a full course of anti-TB therapy but insufficient documentation the investigator should consult with the AbbVie TA MD.

Newly initiated prophylactic treatment should be captured in the eCRF and in the source documents. Prior therapy should be captured in the eCRF.

During the study, subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines and complete at least 6 months of prophylaxis. Study drug(s) should not be withheld and isoniazid should be initiated and 2 to 4 weeks later (per local guidelines), subject should be re-evaluated (unscheduled visit) for signs and symptoms of isoniazid toxicity.

If the subject is experiencing signs or symptoms suspicious for active TB or something has changed in the subject's medical history to warrant a repeat test, the case (including the TB test results) must be discussed with the AbbVie TA MD.

Chest X-Ray

Chest x-ray (posterior-anterior view and lateral view) is required (in Japan and China, a computerized tomography [CT] scan of the chest may be performed in lieu of a chest x-ray, at the investigator's discretion) for all subjects at Screening to rule out the presence of TB or other clinically relevant findings.

The chest x-ray will not be required if the subject had a previous normal chest x-ray (posterior-anterior and lateral views) (or normal CT Scan of the chest) within 90 days of Screening, provided all source documentation is available at the site, as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test.

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

A radiologist or pulmonologist must perform an assessment of the chest x-ray (or CT scan of the chest for subjects in Japan and China). The principal investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the chest x-ray (or CT scan of the chest for subjects in Japan and China) the principal investigator or their designee must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the chest x-ray demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the principal investigator should contact the AbbVie TA MD before enrolling the subject.

12-Lead Electrocardiogram (ECG)

For all subjects, a resting 12-lead ECG will be performed as specified in Appendix C. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. ECGs with QT interval corrected for heart rate using Fridericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed. A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. In cases of QTcF prolongation, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, 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 site monitor 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 source documentation is available and provided nothing has changed in the subject's medical history to warrant a repeat ECG. If there are

other findings that are clinically significant, the investigator must contact the AbbVie TA MD 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.

At Week 12 or Week 24, in the event this may not be performed due to the COVID-19 or any pandemic, the site should perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG.

Height and Weight

Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits, as specified in Appendix C. All measurements will be recorded in metric units where applicable.

Vital Signs

Vital sign determinations of systolic and diastolic BP in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at visits specified in Appendix C. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

Physical Examination

A complete physical examination will be performed at Screening, Baseline, Week 12, and Week 24/PD as specified in Appendix C and must include an assessment of EIMs and fistulas. The physical examination at the Baseline Visit will serve as the baseline physical examination for the entire study. Physical examinations at all other visits (including unscheduled visits) are symptom based and should include the assessment of EIMs, and presence or absence of fistulas as part of calculating the CDAI. The presence or absence of (1) arthritis/arthralgia, (2) iritis/uveitis, and (3) erythema nodosum, pyoderma gangrenosum, and aphthous stomatitis will be collected for the assessment of EIMs.

At Baseline, Week 12, and Week 24/PD, the number of fissures, draining and non-draining enterocutaneous (perianal and abdominal) and rectovaginal fistulas should be recorded, including the number of fistulas draining upon gentle compression. Enterocutaneous fistulas will be considered draining when there is drainage upon gentle compression, and rectovaginal fistulas will be considered draining based on either presence of drainage on physical examination or presence of relevant symptoms (e.g., passage of rectal material or flatus from the vagina). A complete examination of the presence and number of draining and non-draining fistulas during Screening or during the visit for endoscopy at Screening, Week 12, or Week 24/PD may be used for the Baseline, Week 12, or Week 24/PD visits, respectively, and does not need to be repeated at the respective visit.

Physical examination abnormalities noted by the investigator at Baseline prior to the first dose of study drug will be recorded in the subject's medical history; abnormalities noted after the first dose of study drug will be evaluated and documented by the investigator as to whether or not the abnormality is an AE (see Section 6.1.1.1 for AE definition). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

Pregnancy Test

A serum pregnancy test will be performed for all female subjects of childbearing potential at the Screening Visit. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility. If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;

- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

A urine pregnancy test will be performed for all female subjects of childbearing potential at the Baseline Visit prior to the first dose of study drug and at all subsequent visits. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin.

If the baseline or a postbaseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started or resumed. If the serum pregnancy test is positive, study drug must be permanently discontinued. In the event a pregnancy test comes back borderline, a repeat test is required, as described above.

At each visit, the study staff should review the pregnancy avoidance recommendations with each female subject of childbearing potential and document this discussion in the subject's source records.

If during the course of the study a woman becomes surgically sterile or postmenopausal and complete documentation as described in Section 5.2.4 is available, pregnancy testing is no longer requested.

A pregnant or breastfeeding woman will not be eligible for participation in the study or be allowed to continue study drug.

During the COVID-19 or any pandemic-related restrictions, urine pregnancy tests may be performed at the local laboratory or at home and confirmed by site staff via phone,

telemedicine, or video call. Pregnancy test results must be available before drug dispensation.

Hepatitis Screen

All subjects will be tested for the presence of HBV and HCV at Screening.

Hepatitis B

Subjects will be tested for the presence of HBV at screening using the following tests:

- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

HBV serologic test results will be interpreted and managed as shown in Figure 3.

A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will trigger automatic reflex testing for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

For a subject who has had an HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected, the HBV DNA PCR qualitative testing is **not** required and the subject may be enrolled (Scenario B).

A negative test result for HBc Ab does **not** require HBV DNA PCR qualitative testing and the subject may be enrolled (Scenarios A and B).

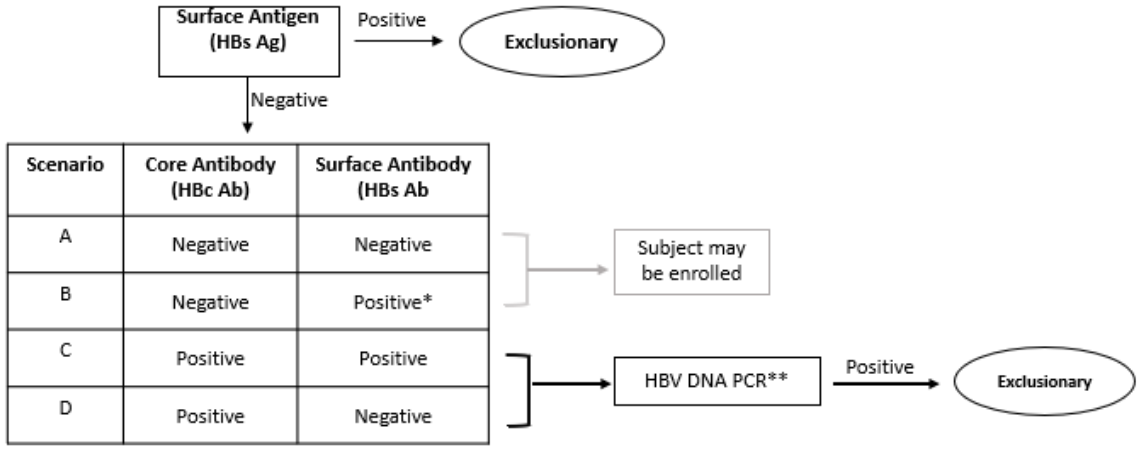
A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Scenarios C and D).

- A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.

- A subject with a negative result for HBV DNA may be enrolled.

Where mandated by local requirements, subjects with positive HBs Ab and/or positive HBc Ab and a negative HBV DNA PCR test at Screening, should have HBV DNA PCR test performed at every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+. In cases where recurrence of HBV DNA is observed, the subject should be discontinued from the study.

Figure 3. Interpretation and Management of HBV Serologic Test Results



DNA = deoxyribonucleic acid, HBV = hepatitis B virus, PCR = polymerase chain reaction

* A positive test result for HBs Ab is expected for subjects who have had a HBV vaccination. For subjects without a history of HBV vaccination (and for subjects in Japan) a positive result for HBs Ab/anti-HBs requires HBV DNA PCR testing.

** In the event that the HBV DNA PCR cannot be performed due to the COVID-19 or any pandemic, perform the HBV DNA PCR at the next earliest feasible visit or arrange to have it completed by a local laboratory.

Hepatitis C

Blood samples for Hepatitis C serology will be obtained at the Screening Visit. A positive HCV Ab will trigger an HCV RNA test. A subject will not be eligible for study participation if test results indicate active Hepatitis C (HCV RNA detectable in any subject with anti HCV Ab).

HIV

Subjects with HIV infection (positive HIV test result) are excluded from study participation. HIV testing will be performed at Screening, unless prohibited by local regulations. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests listed in Table 2 and at visits specified in Appendix C. Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per the investigator's discretion. A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests.

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

Blood draws should be performed, as much as possible, only after all questionnaires, clinical assessments, and vital sign determinations are obtained.

For blood sampling, subjects should be fasting (a minimum 8-hour fast) whenever possible. If a subject is not able to fast when necessary, the non-fasting status will be recorded in study source documentation.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant, the investigator should apply the standard of care for medical evaluation and treatment per local guidelines:

- The investigator will repeat the test to verify the out-of-range value.

- The investigator will follow the out-of-range value to a satisfactory clinical resolution.

A laboratory test value that requires a subject to be discontinued from study drug or requires a subject to receive treatment will be recorded as an AE. Other laboratory abnormalities, including those which meet the toxicity management criteria outlined in Section 6.1.7, may be recorded as AEs at the discretion of the investigator.

Table 2. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**[a]	**Urinalysis**	**Other Laboratory Tests**
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Reticulocyte count Platelet count	BUN Creatinine Total bilirubin ALT AST Alkaline phosphatase CPK Sodium Potassium Chloride Bicarbonate Calcium Inorganic phosphate Uric acid Cholesterol LDL-C HDL-C Triglycerides Total protein Albumin Glucose eGFR[b]	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocytes Nitrites Microscopic examination, if needed **Stool Samples** *C. difficile* toxin Fecal calprotectin	Serum pregnancy (bHCG) test[c] FSH[d] HBs Ag HBs Ab HBc Ab HBV DNA PCR (reflex only) HCV Ab HCV RNA (reflex only) HIV Ab QuantiFERON-TB Gold[e] hs-CRP International Normalized Ratio (INR) (reflex only)[f] Lymphocyte Subsets[g] PK Beta-D-glucan test (Japan only) <u>Local Lab Test:</u> Urine pregnancy test[h]
Additional Samples Collected (Optional)			
Blood, serum, plasma, stool, and intestinal tissue samples for exploratory research,[a] biologic drug level.[i]			

Table 2. Clinical Laboratory Tests (Continued)

ALT = alanine transaminase; AST = aspartate transaminase; bHCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HDL-C = high density lipoprotein cholesterol; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; PCR = polymerase chain reaction; PK = pharmacokinetic; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell

a. Minimum 8-hour fast for chemistry. If a subject is not able to fast when necessary, the non-fasting status will be recorded in study source documentation.
b. eGFR will be done at Screening only.
c. A serum pregnancy test will be performed for all women of childbearing potential at the Screening Visit and if postbaseline urine pregnancy test turns positive.
d. At Screening for female subjects ≤ 55 years old AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined in Section 5.2.4) an FSH should be tested.
e. QuantiFERON-TB Gold is not needed if for some reason PPD is being performed.
f. INR will only be measured if ALT and/or AST > 3 × ULN.
g. Lymphocyte subsets include T (cluster of differentiation [CD]4+ and CD8+) cells, B (CD19+) cells, NK cells, and natural killer T (NKT) cells.
h. A urine pregnancy test will be performed for all female subjects of childbearing potential at the Baseline Visit prior to the first dose of study drug and all subsequent visits.
i. During Screening, biologic drug levels may be optionally assessed at the investigator's discretion as an alternative to completing the required washout period: (1) infliximab and natalizumab: may be tested approximately 4 weeks from the last dose; (2) adalimumab, certolizumab, golimumab, or vedolizumab: may be tested approximately 6 weeks from the last dose; (3) ustekinumab: may be tested approximately 8 weeks from the last dose.

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic or any state of emergency or pandemic situation prevent the subject from having blood drawn for laboratory testing at the study site, if possible, sites should arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. It is recommended to perform all scheduled tests in the protocol, except for hs-CRP, fecal calprotectin, PK, lymphocyte subsets, and optional samples for exploratory research which should not be collected. Local laboratory results should be obtained along with reference ranges and kept within the subject's source documentation. Local laboratory results should be reviewed by the investigator and documented in EDC as an unscheduled laboratory visit as soon as possible.

If it is not possible to perform all of the laboratory tests locally, the minimum laboratory tests presented below should be performed for safety evaluation.

Table 3. Minimum Laboratory Tests for Safety Evaluation

Hematology	Clinical Chemistry	Urine
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count	BUN Creatinine Total bilirubin ALT AST Alkaline phosphatase CPK	Pregnancy test, if applicable Urinalysis, if applicable

ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell

If laboratory samples cannot be obtained, study drug administration may be continued, under some requirements, as described in the Study Drug Dispensing/Administration section below.

Other Laboratory Assessments

High-Sensitivity C-Reactive Protein (hs-CRP)

Blood samples for hs-CRP will be obtained as specified in Appendix C. The hs-CRP results will remain blinded to the sponsor, investigator, study site personnel and the subject. The hs-CRP test will be performed by the central lab.

Local laboratory or site testing for hs-CRP is not allowed after Baseline. Results of hs-CRP may unblind the treatment assignment, and the results may be blunted in subjects taking a JAK inhibitor, thereby limiting clinical utility in the setting of a safety assessment or AE management. Any local testing of hs-CRP or CRP during the placebo-controlled portion of the study is therefore strongly discouraged and any local hs-CRP or

CRP tests reported to the investigator prior to the primary endpoint assessment will be recorded as protocol deviations.

Urinalysis

Dipstick urinalysis (macroscopic analysis) will be completed by the central laboratory at all required visits as listed in Appendix C. A microscopic urinalysis will only be performed by the central laboratory if the dipstick urinalysis results are abnormal, where abnormal is defined as leukocytes, nitrite, ketone, protein, blood, or glucose value of greater than a trace.

Lymphocyte Subsets

Blood samples will be collected at specified visits (Appendix C) to assess lymphocyte subsets: T (CD4+ and CD8+) cells, B (CD19+) cells, NK cells, and NKT cells. These tests will be performed by the central lab.

Stool Samples

Fecal Calprotectin (FCP)

FCP will be performed for all subjects as indicated in Appendix C. Subjects will be asked to provide a stool sample, subjects will be sent home with instructions and a stool sample supplies. All stool samples should be collected before any bowel preparation for endoscopy is started.

The FCP results will remain blinded to the sponsor, investigator, study site personnel and the subject throughout the study. Local laboratory or site testing for FCP is not allowed after Baseline.

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

***Clostridium difficile* Toxin**

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.

If a second sample collection is needed due to unforeseen issues with the first sample (e.g., missing sample, stability issues, inadequate sample, etc.), all efforts must be made to ship the second sample to the central laboratory using dry ice. On an exceptional basis, and after consultation with the AbbVie TA MD, this second sample may be sent to the local lab for testing.

Subjects who are positive for *C. difficile* toxin should be screen-failed; these subjects may be re-screened after completing the appropriate treatment.

Outcomes and Questionnaires

The following outcomes and questionnaires will be completed at the time points as indicated in Appendix C. Refer to Appendix E for descriptions of Patient Reported Outcomes.

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Work Productivity and Activity Impairment Questionnaire (WPAI)-CD
- Crohn's Symptoms Severity Questionnaire (CSS)
- Short Form-36 (SF-36)
- European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Patient Global Impression of Change (PGIC)
- Patient Global Impression of Severity (PGI-S)
- Bristol Stool Chart

During the COVID-19 pandemic or any state of emergency or pandemic situation, when an onsite visit cannot be performed, all questionnaires except EQ-5D-5L scale are eligible for completion by phone or virtual interview. Prior to the phone/virtual visit, the site staff person should be delegated this task on the Delegation of Authority log. Sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites must share a local language version of the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses remotely. The date and start and stop time of PRO data collection should be recorded along with the name of the person who collected the information, their role, and which questionnaires were completed.

Subject Diary

Subjects will be dispensed an electronic diary at Screening and will be trained on how to complete the diary by site staff during the Screening Visit. All subjects should complete their subject diary on a daily basis throughout the entire study. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD Visit, unless the subject continues into Study M14-430.

In case of missing diary information, or when discrepancies are discovered, site personnel should discuss with the subject and document changes in site records, if applicable. Completion will be reinforced during study visits, as necessary.

Remote Visits Due to the COVID-19 or any Pandemic

If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, phone or virtual (remote) visits, or visits at alternative locations may be performed. These visits should occur within 7 days of the planned date, if possible. During these visits, the following procedures should be performed:

- Adverse event assessment

- Concomitant medications
- Compliance to contraception (if applicable)
- Monthly pregnancy testing results (if applicable)
- IP compliance/dosing and drug accountability
- Confirm subject diary entries
- Weight (may be performed by the subject or caregiver)
- Vital signs (may be obtained by the subject or caregiver)
- Questionnaires: All questionnaires except EQ-5D-5L scale are eligible for completion by remote interview at all visits. If there are time constraints to the remote visit, at a minimum, the following must be completed: IBDQ, FACIT-F, PGIC, PGIS.

Assessments that require physical examination (e.g., gentle compression of fistulas, etc.) should not be performed.

The site must keep records of all remote visits.

Study Drug Dispensing/Administration

Study drug will be dispensed to subjects at Baseline, Week 4, and Week 8 in Parts 1 and 2. Subjects that continue into Part 3 will have study drug dispensed at Week 12, Week 16, and Week 20.

Study drug will be taken orally QD beginning at the Baseline visit, and should be taken at approximately the same time each day.

Refer to Section 5.5 for additional information.

If a subject is unable to come to the study site for drug dispensation due to COVID-19 or any pandemic, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable.

DTP study drug shipments will be removed once the pandemic is considered to be resolved.

Study drug may be dispensed, and study drug administration may be continued if laboratory samples cannot be obtained, provided that all the following criteria are met:

1. There is at least 1 post-baseline laboratory assessment,
2. The investigator has reviewed all prior laboratory results and confirms and discusses with the subject via a phone/video call that there is no safety concern for the subject to continue use of the study drug in the absence of current labs,
3. No longer than 6 weeks have passed from the last safety laboratory tests.

Crohn's Disease Activity Index (CDAI)

Average daily very soft or liquid SF, average daily AP score, and well-being will be calculated from the subject diary. During screening subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction based on the Bristol Stool Chart. Physical exam and appropriate laboratory values will be calculated at all study visits, except the 30-day follow-up visit, beginning at Baseline. The Screening period will be a minimum of 8 days to calculate the Baseline scores.

The CDAI scores must be calculated using a hematocrit (Hct) value from the same visit laboratory work. The final CDAI for each visit will be calculated once the Hct value is received from the central lab. If the Hct is missing due to technical issues (e.g., lost sample, clotted sample, etc.), the Hct value from the preceding visit may be used.

Instructions to calculate CDAI

- To answer **questions one (1) through three (3)**, entries from the 7 days prior to the visit should be used as recorded by the subject from the diary.
- Diary entries should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to

endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Diary entries, up to 14 days prior to the visit, will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit. The 7 days do not need to be consecutive.

- In **question four (4)**, for the section 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.
- The evaluation for fever should include all the days that are taken into account for the calculation of the CDAI.
- When completing **question five (5)** ("Taking Lomotil/Imodium/Loperamide/opiates for diarrhea, 0 = no, 1 = yes") on the CDAI, "no" should be answered if a subject is taking an opiate(s) solely for pain. The use of these medications takes into account only the day of the scheduled visit and is only assessing their use as anti-diarrheals.
- For **question seven (7)**, Hct results from central laboratory will be used for the CDAI calculation. If the Hct value contains more than one decimal point, the rounding will be allowed to the tenths decimal (e.g., Hct value 33.44 will be captured as 33.4, Hct value of 33.45 will be captured as 33.5). The Hct values either prior to completing the calculation or at the subtotal box 7 of the CDAI should not be rounded to a whole number.
- For **question eight (8)**, the height obtained at Screening should be used when selecting the standard weight in Appendix H, and this standard weight should be used for calculating every CDAI throughout subject participation in the study.
- Standard height is calculated by using the height obtained at Screening (without shoes) adding 1 inch or 2.5 cm.
- If the body weight obtained at the time of assessment is not captured in kilograms (kg), then when converting into kg, rounding should occur using the second digit after the decimal (also known as the hundredth place) where if the number is 0 – 4, then keep the first digit after the decimal (also known as the tenth place) unchanged. If the second digit after the decimal is 5 – 9, then round up the first digit after the decimal (e.g., 90.246 would be captured as 90.2 and 97.687 would be captured as 97.7).

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

The calculation of the CDAI score is in Appendix I.

Endoscopy

An endoscopy (ileocolonoscopy) will be performed as specified in Appendix C. It is expected that all subjects who remain in the study through at least Week 8 will have a Week 12/PD endoscopy in Part 1 or Part 2. For subjects entering Part 3, it is expected that all subjects who remain in the study through at least Week 20 will have a Week 24/PD endoscopy. An endoscopy performed before the Screening visit, independently of the study, may be used as the Screening endoscopy, with the approval of the AbbVie TA MD, if the following conditions are met:

1. Biopsy confirmation of the diagnosis is available according to section "Biopsy During Endoscopy" below, as applicable.
2. The endoscopy took place within 45 days prior to Baseline 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. In addition, where possible, the investigator or sub-investigator should be the endoscopist for the study.

During the COVID-19 or any pandemic, the Week 12 and Week 24 endoscopies may be performed within 7 days of the planned date if travel restrictions or other pandemic-related reasons impact scheduling. If the endoscopy cannot be performed at the study site, it can be completed at a different hospital/facility.

If the COVID-19 or any pandemic precludes a subject from undergoing an endoscopy at:

- Week 12 or Week 24 and clinical response was achieved, the subject can enroll in Study M14-430.
- Week 12 and clinical response was not achieved, the subject can enter Part 3 of Study M14-431.

All ileocolonoscopies will be performed and recorded at the site in a video format. Sites should also perform the SES-CD assessment and record the findings on the SES-CD score sheet Appendix J and in the appropriate eCRF.

All endoscopies will be reviewed by a central reviewer who is blinded.

There will be a window of 7 days prior to the scheduled visit to conduct the endoscopy, with the exception of the screening endoscopy. This window may be extended as necessary after consultation with the AbbVie TA MD in case of external, not subject-related circumstances (e.g., scheduling conflict).

The endoscopies performed at the time points described above will be used to provide the endoscopy subscores to calculate the SES-CD. All attempts should be made by the endoscopist to explore all segments of the colon and terminal ileum, including intubation of the terminal ileum, at every endoscopy visit. 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.

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 observed area of the colon must be performed during the Screening endoscopy and read by a qualified local pathologist and the results reviewed by the investigator. Biopsies to rule out dysplasia and colon cancer may be taken 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 and kept with the subject's source documents onsite. Subjects should not be enrolled if high grade colonic dysplasia or colon cancer is discovered at Screening endoscopy or endoscopy performed within 45 days prior to Baseline visit. Subjects may be enrolled if low grade colonic dysplasia is discovered during endoscopy and is completely removed.

If a diagnosis of high grade colonic dysplasia or colon cancer is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be recorded as an AE and the subject should be discontinued from the study. If low grade colonic dysplasia is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be entered as an AE and the subject can continue in the study if the lesion has been completely removed.

Subjects who consent to participate in the substudy to collect intestinal biopsies for histologic assessment and exploratory research will have samples collected at Screening, Week 12/PD in Part 1 and Part 2, and Week 24/PD in Part 3, as described in Section 5.3.1.2.1 and the laboratory manual.

Corticosteroid Taper

Subjects who enter the study on oral corticosteroids are not allowed to change the corticosteroid dose during the first 4 weeks of the induction treatment period. Doses of corticosteroids may be decreased during the first 4 weeks only in the event of moderate-to-severe treatment related toxicities.

At Week 4, subjects who are on prednisone (or oral equivalent) or oral budesonide must have their corticosteroid dose tapered according to the proposed schedule in Appendix G. Subjects who enter the study on oral budesonide MMX® (e.g., Cortiment®, Uceris®) or oral beclomethasone must discontinue their corticosteroid at Week 4.

During Part 1 or Part 2, if a subject is unable to tolerate the corticosteroid taper, the subject may have the taper stopped or their corticosteroid dose increased prior to Week 10, per the investigator's discretion, up to the dose used at Baseline. Initiating locally acting (rectal or suppository) or systemic corticosteroids is prohibited during Part 1 or Part 2. Increasing the corticosteroid dose is not allowed at Week 10 through Week 12.

Subjects who do not achieve clinical response at Week 12 and enter in Part 3 and have not completed the corticosteroid taper, must resume and proceed with the taper at Week 16, following the schedule in Appendix G. During Part 3, if a subject is unable to tolerate the corticosteroid taper, the subject may have the taper stopped or their corticosteroid dose increased prior to Week 22, per the investigator's discretion, up to the dose used at Baseline. Increasing the corticosteroid dose is not allowed at Week 22 through Week 24. Initiating locally acting (rectal or suppository) or systemic corticosteroids is prohibited during Part 3.

Optional Home Healthcare Service Due to the COVID-19 Pandemic or a State of Emergency or Pandemic Situation

Subjects may be offered the option of home healthcare visits provided by a study nurse or third-party vendor. Study procedures conducted in the home setting may include vital signs, weight, physical examination, safety assessments, compliance to ePRO entries, study medication and contraception, pregnancy test, ECG, blood/stool/urine sample collection, if applicable. This option can only be offered in countries and sites that comply with local regulatory and IRB/IEC requirements for home care. Any pre-requisite submissions or notifications to the site IRB/IEC and local competent health authority

should be made, and approvals must be obtained prior to implementation. The investigator should be available via phone call if a consultation is necessary.

Finally, it is recommended that medical personnel entering a subject's home adhere to local health regulations during the pandemic, such as the use of Personal Protective Equipment (PPE), as required.

Sites may perform home healthcare visits after the following requirements are met:

1. Confirmation that the subjects study safety assessments have been reviewed by the principal investigator and that home assessment is appropriate.
2. Confirmation that the subject's written consent to home healthcare has been obtained. If the home visits will not be performed by site personnel, the site may be responsible for selecting a vendor, contracting with a vendor, and for ensuring continued compliance with the terms of the Clinical Study Agreement.

5.3.1.2 Collection and Handling of Optional Samples for Exploratory Research

Subjects will have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research. The procedures for obtaining and documenting informed consent are discussed in Section 9.3.

AbbVie (or people or companies working with AbbVie) will store the exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on upadacitinib (or drugs of this class) or CD and related conditions continues, but for no longer than 20 years after study completion.

The following samples will be collected according to Appendix C from each subject who consents to provide samples for exploratory research:

- Blood samples for pharmacogenetic and epigenetic analyses (DNA)
- Blood samples for transcriptomic and/or epigenetic analyses (RNA) if possible
- Serum and plasma samples for systemic analyses including, but not limited to, proteomics and metabolomics
- Stool samples for biomarker analyses including but not limited to proteomics and microbiota analysis in approximately 200 subjects (fecal biomarker substudy).

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

5.3.1.2.1 Optional Samples for Histology Exploratory Research

Optional intestinal biopsy samples for histopathology and biological investigations, including but not limited to, transcriptomic analyses and immunohistochemistry may be evaluated in approximately 200 subjects (intestinal biopsy substudy). Samples will be collected according to Appendix C.

Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for assay of upadacitinib will be collected at each visit beginning at Week 2. On the Week 4 visit day, if possible, subjects should take the oral study drug dose at the clinic after collecting the PK blood sample, except if the subjects regularly take the study drug dose at night. Those subjects who regularly take the oral study drug dose at night should continue to take oral study drug according to their normal schedule. For all other visits, subjects can take the oral study drug dose on visit days at their regular schedule and not necessarily at the clinic.

For all PK samples, the date and accurate time of the PK sample collection will be recorded on the lab requisition form. The date and accurate time of the last two study drug doses will be recorded on the eCRF to the nearest minute.

Blood samples for the screening of prior biologics treatment (infliximab, natalizumab, adalimumab, certolizumab, golimumab, vedolizumab, or ustekinumab) may be collected at the discretion of the investigator according to Appendix C.

5.3.2.2 Handling/Processing of Samples

Detailed instructions for the handling and processing of plasma and serum samples will be provided by the central laboratory. The plasma samples will be shipped to the central laboratory. Upadacitinib plasma concentration will be determined at AbbVie.

Instructions for the preparation and shipment of samples will be provided in the laboratory manual. The serum samples for biologics testing will be shipped to the central lab.

5.3.2.3 Disposition of Samples

The frozen plasma samples for upadacitinib assays and samples for biologics testing 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.

5.3.2.4 Measurement Methods

Plasma concentrations of upadacitinib will be determined under the supervision of the Drug Analysis Department at AbbVie using validated liquid chromatography/mass spectrometry methods. Any additional metabolite(s) may be analyzed using non-validated methods.

Serum levels of biologics will be determined under the supervision of the drug analysis department at AbbVie.

5.3.3 Efficacy Variables

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

- **Clinical remission per PROs:** average daily very soft or liquid SF ≤ 2.8 AND average daily AP score ≤ 1.0 and both not greater than Baseline
- **Clinical remission per CDAI:** CDAI < 150
- **Enhanced Clinical Response:** ≥ 60% decrease in average daily very soft or liquid SF and/or ≥ 35% decrease in average daily AP score and both not greater than baseline, or clinical remission
- **Clinical response 100 (CR-100):** decrease of at least 100 points in CDAI from Baseline
- **Clinical response:** ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP score and both not greater than Baseline
- **Endoscopic remission:** SES-CD ≤ 4 and at least 2 point reduction from Baseline and no subscore > 1 in any individual variable, as scored by central reviewer
- **Endoscopic response:** decrease in SES-CD > 50% from Baseline of the induction study (or for subjects with an SES-CD of 4 at Baseline, at least a 2 point reduction from Baseline), as scored by central reviewer

5.3.3.1 Part 1 Primary Variables

The co-primary and ranked secondary endpoints will be analyzed separately for EU/EMA and US/FDA regulatory purposes. The endpoints are specified separately for each set of analyses.

Co-primary endpoints for EU/EMA regulatory purposes:

1. Proportion of subjects with clinical remission per PROs at Week 12, and
2. Proportion of subjects with endoscopic response at Week 12.

Co-primary endpoints for US/FDA regulatory purposes:

1. Proportion of subjects with clinical remission per CDAI at Week 12, and
2. Proportion of subjects with endoscopic response at Week 12.

5.3.3.2 Part 1 Secondary Variables

5.3.3.2.1 Ranked Secondary Variables

The ranked secondary endpoints for EU/EMA regulatory purposes are as follows:

1. Proportion of subjects with clinical remission per CDAI (CDAI < 150) at Week 12
2. Proportion of subjects with clinical remission per PROs at Week 4
3. Proportion of subjects with endoscopic remission at Week 12
4. Proportion of subjects who discontinue corticosteroid use for CD and achieve clinical remission per PROs at Week 12, in subjects taking corticosteroids for CD at Baseline
5. Change from Baseline in FACIT-F at Week 12
6. Change from Baseline in IBDQ at Week 12
7. Proportion of subjects achieving CR-100 at Week 2
8. Proportion of subjects achieving CR-100 at Week 12
9. Proportion of subjects with hospitalizations due to CD during the 12 week double-blind induction period
10. Proportion of subjects with resolution of EIMs at Week 12, in subjects with EIMs at Baseline.

The ranked secondary endpoints for US/FDA regulatory purposes are as follows:

1. Proportion of subjects with clinical remission per PROs at Week 12

2. Proportion of subjects with endoscopic remission at Week 12
3. Proportion of subjects who discontinue corticosteroid use for CD and achieve clinical remission per CDAI at Week 12, in subjects taking corticosteroids for CD at Baseline
4. Change from Baseline in FACIT-F at Week 12
5. Change from Baseline in IBDQ at Week 12
6. Proportion of subjects achieving CR-100 at Week 2
7. Proportion of subjects achieving CR-100 at Week 12
8. Proportion of subjects with clinical remission per CDAI at Week 4
9. Proportion of subjects with hospitalizations due to CD at during the 12-week double-blind induction period
10. Proportion of subjects with resolution of extra-intestinal manifestation (EIM) at Week 12, in subjects with EIM at Baseline.

5.3.3.2.2 Additional Efficacy Variables

Non-ranked endpoints are as follows:

- Proportion of subjects:
  - with clinical remission per PROs over time
  - with clinical remission per CDAI (CDAI < 150) over time
  - with enhanced clinical response over time
  - with clinical response over time
  - with CR-100 over time
  - with clinical remission per PROs and endoscopic remission at Week 12
  - with clinical remission per CDAI and endoscopic remission at Week 12
  - with enhanced clinical response and endoscopic response at Week 12

- who discontinue corticosteroid use for CD and achieve endoscopic remission at Week 12, in subjects taking corticosteroids for CD at Baseline
- who discontinue corticosteroid use for CD and achieve enhanced clinical response at Week 12, in subjects taking corticosteroids for CD at Baseline
- who discontinue corticosteroid use for CD and achieve endoscopic response at Week 12, in subjects taking corticosteroids for CD at Baseline
- who discontinue corticosteroid use for CD at Week 12, in subjects taking corticosteroids for CD at Baseline
- with ≥ 50% reduction in the corticosteroid dose for CD from Baseline at Week 12, in subjects taking corticosteroids for CD at Baseline
- with hospitalizations during the 12 week double-blind induction period
- undergoing CD-related surgeries during the 12 week double-blind induction period
- decrease in SES-CD > 50% from Baseline of the induction study or endoscopic remission at Week 12, as scored by central reviewer
- with SES-CD ≤ 2 at Week 12
- with SES-CD ulcerated surface subscore of 0 at Week 12 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline, as scored by a central reviewer
- with SES-CD ulcerated surface subscore ≤ 1 in each segment at Week 12 in subjects with a SES-CD ulcerated surface subscore ≥ 2 at Baseline, as scored by a central reviewer
- with endoscopic remission at Week 12 among subjects with SES-CD subscore of 3 in the narrowing component at Week 12, which was not present at Baseline
- with endoscopic response at Week 12 among subjects with SES-CD subscore of 3 in the narrowing component at Week 12, which was not present at Baseline
- with endoscopic response or endoscopic remission at Week 12 among subjects with SES-CD subscore of 3 in the narrowing component at Week 12, which was not present at Baseline

- with endoscopic remission at Week 12 among subjects with SES-CD narrowing component subscore between 0 and 2 in all intestinal segments at Baseline
- with endoscopic response at Week 12 among subjects with SES-CD narrowing component subscore between 0 and 2 in all intestinal segments at Baseline
- with endoscopic response or endoscopic remission at Week 12 among subjects with SES-CD narrowing component subscore between 0 and 2 in all intestinal segments at Baseline
- achieving Colonic and Ileal Global Histologic Disease Activity Score (CGHAS/IGHAS) histologic remission (defined as CGHAS/IGHAS score ≤ 3 in those with abnormal histology at Baseline) at Week 12
- without draining fistulas at Week 12 in subjects with draining fistulas at Baseline
- with $\geq 50\%$ reduction in draining fistulas at Week 12, in subjects with draining fistulas at Baseline
- with at least 50% decrease in the number of days with very soft or liquid stools (Type 6 or 7, per Bristol Stool Chart) during the last 7 days at Week 12
- with IBDQ remission (IBDQ $\geq$ 170 points) over time
- with IBDQ response (increase in IBDQ $\geq$ 16 points from Baseline) over time
- achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) over time.
- achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 12

- Change from Baseline in:
  - IBDQ over time
  - individual IBDQ domain scores (bowel, emotional, social, systemic) over time
  - individual IBDQ item under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29) over time

- WPAI-CD over time
- EQ-5D-5L over time
- SF-36 over time
- CSS over time
- FCP over time
- hs-CRP over time
- average daily AP score over time
- average daily very soft or liquid SF over time
- average daily total SF over time
- CDAI over time
- SES-CD at Week 12
- mean CGHAS/IGHAS at Week 12 among subjects with abnormal histology at Baseline

5.3.3.3 Part 2 Variables

Same efficacy endpoints as those listed in Part 1 (Section 5.3.3.1 and Section 5.3.3.2) are considered for Part 2 of the study. All the Part 2 efficacy endpoints are considered additional endpoints and ranking of the endpoints is not applicable for Part 2.

5.3.3.4 Part 3 Variables

- Proportion of subjects:
  - with clinical remission per PROs over time
  - with clinical remission per CDAI (CDAI < 150) over time
  - with enhanced clinical response over time
  - with clinical response over time
  - with endoscopic remission at Week 24
  - with clinical remission per PROs and endoscopic remission at Week 24
  - with clinical remission per CDAI and endoscopic remission at Week 24
  - with enhanced clinical response and endoscopic response at Week 24

- who discontinue corticosteroid use for CD and achieve clinical remission per PROs at Week 24, in subjects taking corticosteroids for CD at Week 12
- who discontinue corticosteroid use for CD and achieve clinical remission per CDAI at Week 24, in subjects taking corticosteroids for CD at Week 12.
- who discontinue corticosteroid use for CD and achieve endoscopic remission at Week 24, in subjects taking corticosteroids for CD at Week 12
- who discontinue corticosteroid use for CD and achieve enhanced clinical response at Week 24, in subjects taking corticosteroids for CD at Week 12
- who discontinue corticosteroid use for CD and achieve endoscopic response at Week 24, in subjects taking corticosteroids for CD at Week 12
- who discontinue corticosteroid use for CD at Week 24, in subjects taking corticosteroids for CD at Week 12
- with ≥ 50% reduction in the corticosteroid dose for CD from Baseline at Week 24, in subjects taking corticosteroids for CD at Week 12
- with hospitalizations due to CD during Part 3
- with hospitalizations during Part 3
- undergoing CD-related surgeries during Part 3
- with resolution of EIMs at Week 24, in subjects with EIMs at Baseline or Week 12
- decrease in SES-CD > 50% from Baseline of the induction study or endoscopic remission at Week 24, as scored by central reviewer
- with SES-CD ≤ 2 at Week 24
- with SES-CD ulcerated surface subscore of 0 at Week 24 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline, as scored by a central reviewer
- with SES-CD ulcerated surface subscore ≤ 1 in each segment at Week 24 in subjects with a SES-CD ulcerated surface subscore ≥ 2 at Baseline, as scored by a central reviewer
- achieving (CGHAS/IGHAS) histologic remission (defined as CGHAS/IGHAS score ≤ 3 in those with abnormal histology at Baseline) at Week 24

  - with ≥ 50% reduction in draining fistulas at Week 24, in subjects with draining fistulas at Baseline
  - without draining fistulas at Week 24 in subjects with draining fistulas at Baseline or Week 12
  - with at least 50% decrease in the number of days with very soft or liquid stools (Type 6 or 7, per Bristol Stool Chart) during the last 7 days at Week 24.
- Change from Baseline in:
  - IBDQ over time
  - WPAI-CD over time
  - EQ-5D-5L over time
  - CSS at Week 24
  - FACIT-F at Week 24
  - SF-36 at Week 24
  - FCP over time
  - hs-CRP over time
  - average daily AP score over time
  - average daily very soft/liquid SF over time
  - average daily total SF over time
  - CDAI over time
  - SES-CD at Week 24
  - mean CGHAS/IGHAS at Week 24 among subjects with abnormal histology at Baseline
- Time to:
  - clinical response
  - enhanced clinical response
  - clinical remission

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Plasma upadacitinib concentrations will be obtained at the times indicated in Appendix C. 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 upadacitinib oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

5.3.6 Optional Exploratory Research Variables

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may be analyzed for genetic factors contributing to the subject's response to study treatment, in terms of pharmacokinetics, 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 drug response. Genomic testing and analysis may involve (but is not limited to) sequencing of single nucleotide polymorphisms (SNPs), whole exomes, whole genomes and epigenetics. RNA testing and analysis may involve (but not limited to) sequencing and expression of all classes (i.e., microRNA [miRNA], long non-coding RNA [lncRNA], piwi interacting RNA [piRNA] etc.) of RNA. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects can request to be discontinued from participating in the study at any time for any reason including but not limited to disease progression or lack of response to treatment. The investigator may discontinue any subject's participation for any reason, including but not limited to disease progression, lack of response to treatment, an AE, safety concerns, or failure to comply with the protocol. See Section 6.1.7 for toxicity management criteria.

Subjects will have study drug discontinued immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Serious infections (e.g., sepsis), which would put the subject at risk for continued participation in the trial as determined by the investigator.
- The investigator believes it is in the best interest of the subject, including subjects with no improvement to study drug at Week 12 for whom the investigator believes it is not in the best interest of the subject to enter in the Extended Treatment Period.
- The subject requests withdrawal from the study.
- Inclusion or 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 TA MD.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie TA MD.
- 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 drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.

- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation in the trial as determined by the investigator or the AbbVie TA MD.
- Subject develops a gastrointestinal perforation (other than appendicitis or mechanical injury).
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, nonneurologic arterial thrombosis. See Section 6.1.7 Toxicity Management.

During the COVID-19 pandemic or any state of emergency or pandemic situation, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. The investigator should contact the AbbVie TA MD before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment or study participation should complete a PD visit as described in Section 5.1.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. 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 study drug, the subject will be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

Lost to Follow-Up

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

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be taken orally QD, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day. The study drug can be taken with or without food. Subjects will continue their stable background CD therapy, if allowed per protocol. AbbVie will not supply any background CD therapy taken during the course of the study.

Study drug may be shipped from the study site directly to the study subject's home if all of the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee.
- Subject agrees to have the study drug shipped directly to their home.
- Shipments may also include other study supplies (e.g., paper copies of PROs, urine pregnancy tests). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to pandemic-

related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

- AbbVie will not receive subject identifying information related to these shipments as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 4.

Table 4. Identity of Investigational Product

Investigational Product	Dosage Form	Strength	Route of Administration
Upadacitinib	Film-coated tablet	45 mg	Oral
Matching placebo	Film-coated tablet	NA	Oral
Upadacitinib	Film-coated tablet	30 mg	Oral

5.5.2.1 Packaging and Labeling

Upadacitinib and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit label will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (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 kits. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug(s)

Study drugs must be stored at controlled room temperature (15° to 25°C/59° to 77°F). 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 as appropriate.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique identification number by the IRT at the Screening visit and will keep the same unique subject identification number throughout the study. Subjects who meet all of the inclusion criteria and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized.

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 drug should not be re-dispensed to any subject.

In Part 1, subjects (n = 495) will be randomized in a 2:1 ratio to upadacitinib 45 mg QD or matching placebo for 12 weeks (Figure 1). The randomization will be stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologic treatments (> 1 and ≤ 1).

At Week 12, subjects achieving clinical response, defined as ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP score (both not worse than Baseline) may be eligible to enter the 52-week double-blind maintenance portion of Study M14-430.

Part 2 is an open-label portion of this study. Once enrollment in Part 1 is complete, approximately 130 subjects will be enrolled to receive upadacitinib 45 mg QD for 12 weeks (Figure 1). The objective of Part 2 is to have a sufficient number of subjects with clinical response to be re-randomized in the double-blind maintenance portion of

Study M14-430, while minimizing unnecessary exposure to placebo. At Week 12, subjects achieving clinical response may be eligible to enter Study M14-430.

Subjects who do not achieve clinical response at Week 12 in Part 1 or Part 2 will be able to participate in Part 3 (Extended Treatment Period) and receive upadacitinib for 12 weeks until Week 24/PD. The objectives of Part 3 are to offer blinded upadacitinib induction treatment to placebo non-responders from Part 1 and to evaluate a delayed clinical response to upadacitinib in subjects who did not initially respond to upadacitinib during Part 1 or Part 2. Part 3 consists of 3 cohorts, and the treatment assignment will depend on the treatment received in Part 1 or Part 2, as follows:

- **Cohort 1:** Subjects who received placebo in Part 1 and did not achieve clinical response at Week 12 are eligible to receive double-blind induction treatment with upadacitinib 45 mg QD.
- **Cohort 2:** Subjects who received double-blind upadacitinib in Part 1 and did not achieve clinical response at Week 12 are eligible to receive double-blind upadacitinib 30 mg QD.
- **Cohort 3:** Subjects who received open-label upadacitinib during Part 2 and did not achieve clinical response at Week 12 are eligible to receive open-label upadacitinib 30 mg QD.

Subjects in Cohort 1 and 2 will remain blinded to treatment to avoid unmasking the treatment received during Part 1. Subjects are not eligible to enter in Part 3 until the Week 12 endoscopy has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, the subject can continue in Part 3.

At Week 24, subjects who achieve clinical response may be eligible to enter Study M14-430. Subjects are not eligible to enter Study M14-430 until the ileocolonoscopy procedure at Week 24 for evaluation of mucosal inflammation has been completed. If the COVID-19 pandemic precludes a subject from undergoing an endoscopy, the subject can enroll in Study M14-430 if clinical response was achieved at Week 24.

Subjects who do not achieve clinical response at Week 24 will be discontinued from Study M14-431 and will receive standard of care treatment at the investigator's discretion. Subjects who do not achieve clinical response at Week 24 and all subjects who prematurely discontinue the study will have a follow-up visit 30 days from the last dose of study drug to collect information on new or ongoing AEs and laboratory assessments.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in Section 5.5.1.

On dosing days that occur on study visit days, subjects should follow the regular dosing schedule (refer to Section 5.3.2.1 regarding Week 4 visit).

Each subject's dosing schedule should be closely monitored by the site at each study visit. This will ensure that all subjects enrolled into the study maintain their original dosing schedule beginning with the first dose of study drug (Baseline/Day 1).

If a subject should forget to take their upadacitinib (or matching placebo) 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 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.

For elective and emergency surgeries, the following rules apply:

- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
- Elective surgery will not be allowed during the study until the primary endpoint has been assessed. If the subject undergoes elective surgery, the study drug should be interrupted 1 week prior to the planned surgery. Reintroduction of study drug is allowed once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

5.5.5 Blinding

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study and until that data is locked and analyzed as part of the planned analysis. In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of medical emergency.

In the event of a medical situation that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/help-desk/.

In the event that the blind is broken before notification to the AbbVie TA MD, we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

5.5.5.1 Blinding of Investigational Product

In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study will be identical in appearance.

5.5.5.2 Blinding of Data for Data Monitoring Committee (DMC)

An external DMC comprised of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. 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 describe the roles and responsibilities of the DMC members, frequency and triggers of data reviews, relevant safety data to be assessed, and communication with and recommendations to AbbVie as well as relevant competent authorities, if necessary.

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess cardiovascular AEs and embolic and thrombotic events (non-cardiac, non-central nervous system) in a blinded manner as defined by the cardiovascular adjudication committee (CAC) charter.

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

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.

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.

Subjects will be counseled on missed doses of study drug. If the subject does not return the bottles (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug. The information should be

documented on the source documents as per "best recollection" before completing on the applicable eCRF page.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document and by registering the arrival of drug through the IRT. The original Proof of Receipt Note and the IRT confirmation sheet will be kept in the site files as a record of what was received.

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 the person dispensing the drug.

All empty/used study drug packaging will be inventoried by the site. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary.

Site staff will complete study drug accountability via IRT, by using source documents, and by visually inspecting the packaging whenever possible. After drug accountability has been completed, used packaging and unused study drug will be destroyed on site according to local procedures or regulations or returned to the destruction depot (for those sites that do not meet AbbVie's documentation requirements for on-site destruction). The use of a third party vendor for drug destruction must be pre-approved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

During the COVID-19 or any pandemic, if a visit is completed virtually, study drug accountability can be conducted remotely with the subject. Any kits that are accounted for remotely should be retained by the subject and when the subject is then able to

complete an onsite visit, they should return all kits for verification of the drug accountability by the site staff.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Upadacitinib is a novel, orally administered JAK1 inhibitor being developed for the treatment of adult patients with inflammatory diseases and may provide improved clinical benefit to CD patients. The proposed study is a Phase 3, randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib in adult subjects with a confirmed diagnosis of CD for at least 3 months and moderately to severely active CD who have inadequately responded to or are intolerant to biologic therapy. This study will evaluate one induction dose of upadacitinib 45 mg QD.

In Part 1, subjects (n = 495) will be randomized in a 2:1 ratio to 45 mg upadacitinib QD or matching placebo for 12 weeks. The randomization will be stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologic treatments (> 1 and ≤ 1). At this time, a 12-week placebo-controlled study is necessary for registrational purposes. A comparative study utilizing placebo provides an unbiased assessment of the efficacy and safety profile of upadacitinib.

Part 2 is an open-label portion (open-label cohort) of this study. Once enrollment in Part 1 is complete, approximately 130 subjects will be enrolled to receive upadacitinib 45 mg QD for 12 weeks. The objective of Part 2 is to have a sufficient number of subjects with clinical response to be re-randomized in the double-blind maintenance portion of Study M14-430, while minimizing unnecessary exposure to placebo.

To ensure all subjects are given the opportunity to receive potentially efficacious therapy, all subjects in Part 1 or Part 2 who do not achieve clinical response after 12 weeks will be able to enroll in Part 3, an Extended Treatment Period for 12 weeks. Part 3 consists of 3 cohorts. The first objective of Part 3 is to offer blinded upadacitinib induction treatment

to placebo non-responders from Part 1. In the upadacitinib Phase 2 Study M13-740, some subjects achieved clinical remission between Week 12 and Week 16 with upadacitinib 6 mg BID, 24 mg BID and 24 mg QD. This study will also evaluate delayed clinical response to upadacitinib in subjects who did not initially respond to upadacitinib 45 mg QD during Part 1 or Part 2. In Part 3, these subjects will receive upadacitinib 30 mg QD for an additional 12 weeks.

The study was designed to enroll 625 subjects to meet scientific and regulatory objectives, without enrolling an undue number of subjects in alignment with ethical considerations.

5.6.2 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 will increase study rigor and ensure enrollment of patients with moderately to severely active CD.

5.6.3 Suitability of Subject Population

Adult male and female subjects between 18 to 75 years of age (or minimum age of adult consent according to local regulations) with moderately to severely active CD, who meet all of the inclusion criteria and none of the exclusion criteria, are eligible for enrollment in this study. The specific population chosen was based on the unmet medical need of subjects with a history of inadequate response or intolerance to biologic therapy.

5.6.4 Selection of Doses in the Study

This study will evaluate one induction dose of upadacitinib (45 mg QD) (Figure 1). The selection of this dose was informed by the analysis of the 16-week safety, efficacy and exposure-response data of Phase 2 CD Study M13-740, which evaluated 5 induction doses of upadacitinib using the immediate-release formulation (3, 6, 12 or 24 mg BID or 24 mg QD) versus placebo. In addition, all of the currently available PK, pharmacodynamic, safety, and efficacy data from upadacitinib studies were used to

support the selection of this dose. The induction phase results from Study M13-740 demonstrated the clinical and endoscopic efficacy of upadacitinib compared to placebo with doses of 6 mg BID and higher.

Upadacitinib dose of 45 mg QD using the once-daily formulation provides equivalent daily area under the concentration-time curve (AUC) and comparable maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) to 18 mg BID dose using the immediate-release formulation. In the CD Phase 2 study, the dose of 12 mg BID and higher were shown to approach the plateau of efficacy for clinical endpoints while increasing the dose to 24 mg BID provided additional efficacy benefit particularly for the endoscopic endpoints. Therefore, 45 mg QD regimen using the once-daily formulation (equivalent to 18 mg BID immediate-release) is predicted to provide the optimal balance between maximizing efficacy while limiting the effects on laboratory parameters (e.g., decreases in hemoglobin and NK cells). Upadacitinib 45 mg QD, dosed for up to 12 weeks is expected to be efficacious with an acceptable safety profile and upadacitinib 15 mg QD and 30 mg QD, dosed for up to 240 weeks as maintenance treatment, are expected to be efficacious with acceptable safety profiles.

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 AEs, please refer to Sections 6.1 through 6.1.9. 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 AEs on a routine basis throughout the study. The investigator will assess and record any AE in

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

All AEs will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE 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 AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition or 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 AE.

6.1.1.2 Serious Adverse Events

If an AE 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 SAE.

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 (ADL) 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 SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF.

6.1.1.3 Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study (see detailed toxicity management in Section 6.1.7):

- Serious infections;
- Opportunistic infections;
- Herpes zoster;
- Active TB;
- Malignancy (all types);
- Adjudicated gastrointestinal perforations;
- Adjudicated cardiovascular events (e.g., major adverse cardiac event [MACE]);
- Anemia;
- Neutropenia;
- Lymphopenia;
- Renal dysfunction;

- Hepatic disorder;
- Elevated CPK;
- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system [CNS]).

6.1.2 Adverse Event Severity

When criteria are available, events should be graded as described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

If no grading criteria are provided for the reported event, then the event should be graded as mild, moderate, or severe per the investigator's judgment.

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate (Grade 2)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Severe (Grade 3-5)	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

Use the following guidelines when entering the severity grading criteria into the electronic data capture (EDC) system: Grade 1 as Mild; Grade 2 as Moderate; and Grade 3 to 5 as severe.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the AE 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 causality or deemed it not assessable, AbbVie will consider the event associated.

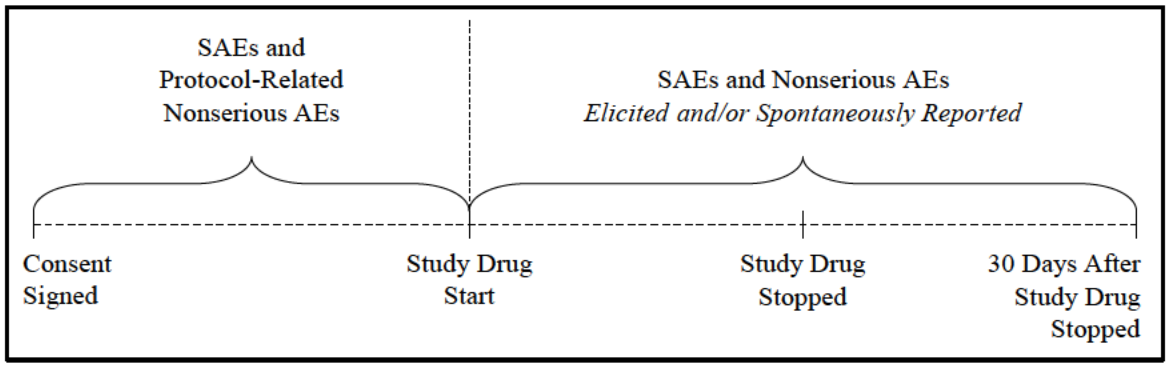
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the SAE.

6.1.4 Adverse Event Collection Period

All AEs 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. Subjects who discontinue study drug treatment but continue to participate in the study will have SAEs and nonserious AEs collected for the remainder of study participation. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signed the study-specific informed consent.

AE information will be collected as shown in Figure 4.

Figure 4. Adverse Event Collection



AE = adverse event; SAE = serious adverse event

Additionally, in order to assist the adjudication process, additional information on any potential MACE will be collected, if applicable.

In case of any of the following reported events, an appropriate supplemental cardiovascular events eCRF should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack.

In case of a reported AE of herpes zoster infection, or a non-cardiac, non-CNS embolic or thrombotic event, a Supplemental AE eCRF should be completed.

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

Events of COVID-19 should be captured as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and above.

COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

6.1.5 Adverse Event Reporting

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. SAEs 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 the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
1 North Waukegan Road
North Chicago, IL 60064

Office: (833) 942-2226
Email: SafetyManagement_Immunology@abbvie.com

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

Primary Therapeutic Area Medical Director:

[redacted]
AbbVie, Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Phone:
Cell:
Fax:
Email: [redacted]

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

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product 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 upadacitinib Investigator's Brochure.

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

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 from study drug (Section 5.4.1).

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

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

6.1.7 Toxicity Management

The toxicity management of the AEs including AEs of special interest consists of safety monitoring (review of AEs on an ongoing basis, and periodical/ad hoc review of safety issues by a safety DMC), interruption of study drug dosing with appropriate clinical management if applicable, and discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

For subjects who discontinued study drug but continued study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central lab) and any intolerability to standard of care therapies should be managed by the prescribing physician.

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. 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. Study drug may be resumed once the infection has been successfully treated. Subjects who develop active TB must be discontinued from study drug.

Herpes zoster: If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a gastrointestinal perforation should be evaluated promptly for early diagnosis and treatment. If the diagnosis of gastrointestinal perforation is confirmed (other than appendicitis or mechanical injury), the subject must be discontinued from study drug.

Cardiovascular Events (MACE): Subjects presenting with potential cardiovascular events should be appropriately assessed and carefully monitored. These events will be reviewed and adjudicated by an independent Cardiovascular Adjudication Committee (CAC) in a blinded manner.

Thrombosis Events: Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolus or noncardiac, nonneurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The COVID-19 eCRF form must be completed.

Malignancy: Subjects who develop malignancy or high grade colonic dysplasia, other than NMSC or carcinoma in situ of the cervix must be discontinued from study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at increased risk for skin cancer.

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug.

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 following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 5 and may

require an appropriate supplemental eCRF to be completed. All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to satisfactory resolution. If a repeat test is required per Table 5, the repeat testing must occur as soon as possible.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, or the hemoglobin value remains in the normal reference range, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
ANC	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its baseline value. • Interrupt study drug if confirmed < 500/µL by repeat testing with new sample. If value returns to normal reference range or its Baseline value, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
ALC	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its baseline value.
Total WBC count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until WBC count returns to normal reference range or its baseline value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5. o A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. o Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from Baseline). • Interrupt study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. • Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. Subjects with positive HBc Ab (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following laboratory findings should have HBV DNA by PCR performed within 1 week (based on initial elevated value): o ALT > 5 × ULN OR o ALT/AST > 3 × ULN if an alternative cause is not readily identified • A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST. A positive result for HBV DNA PCR testing in these subjects will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found and ALT or AST elevations persist. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason rechallenge is expected to be safe. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and > ULN, repeat the test for serum creatinine (with subject in a euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion then interrupt study drug and restart study drug once serum creatinine returns to ≤ 1.5 × baseline value and ≤ ULN. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
CPK	• If any confirmed CPK value ≥ 4 × ULN (if symptomatic or asymptomatic). • If confirmed CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. For the above CPK elevation scenarios, complete supplemental CPK eCRF.

6.1.8 Data Monitoring Committee (DMC)

An external, independent DMC will be responsible for monitoring unblinded safety data and alerting AbbVie to possible safety concerns related to the conduct of the study. See Section 5.5.5.2 for details.

6.1.9 Cardiovascular Adjudication Committee (CAC)

An independent committee of physician experts in cardiac adjudication will be utilized to assess cardiovascular AEs and embolic and thrombotic events (non-cardiac, non-CNS) in a blinded manner as defined by the CAC charter. The events that are adjudicated and the adjudication process will be detailed in the CAC Charter. Dedicated eCRFs will be used for events of myocardial infarction-unstable angina, stroke-transient ischemic attack, and death. In addition, the site may be contacted for additional source documentation for relevant events.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the 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 (e.g., 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 AEs 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 unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified), including those that may be due to the COVID-19 or any pandemic or any state of emergency situation after a subject has been enrolled, the principal investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), their assigned contract research organization Clinical Monitor or the following AbbVie Clinical Monitors:

Primary Contact:

[redacted]
AbbVie, Inc.
1 North Waukegan Rd
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]
Fax:

Alternate Contact:

[redacted]
AbbVie, Inc.
1 North Waukegan Rd
[redacted]
North Chicago, IL 60064
USA

Office: [redacted]
Fax:

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.

In Japan, the investigator will record all protocol deviations in the appropriate medical records at site.

- 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 Analytical Plans

The objective of the statistical analysis of Study M14-431 is to evaluate the efficacy and safety of an upadacitinib 45-mg QD induction dose versus placebo in subjects with moderately and severely active CD.

The extent of missing data due to COVID-19 will be monitored and appropriate analysis to handle these missing data may be performed; details will be included in the SAP. Further details of the statistical analysis will be described and documented in the Statistical Analysis Plan (SAP).

8.1.1 Datasets for Analysis

8.1.1.1 Intent to Treat Analysis Set

The intent-to-treat (ITT) analysis set includes all randomized subjects who have received at least one dose of study drug in the double-blind induction period from Part 1. The ITT subjects will be analyzed as randomized. The ITT set is the primary population for efficacy analysis. All analyses of efficacy endpoints will be performed using the ITT analysis set.

8.1.1.2 Safety Analysis Set

The safety analysis set consists of all subjects who received at least one dose of the study drug. Similarly, safety analysis set (Part 1), safety analysis set (Part 2), and safety analysis set (Part 3) consist of subjects who received at least one dose of the study drug, enrolled in Part 1, Part 2, and Part 3 respectively. The safety analysis set and safety analysis sets (Part 1, Part 2 and Part 3) will be analyzed as treated, according to treatment

the subject actually received. The safety analysis set and safety analysis sets (Part 1, Part 2 and Part 3) will be used for safety analysis.

8.1.2 Definition of Missing Data Imputation

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

Non-Responder Imputation (NRI): The NRI approach is used for binary efficacy variables. These variables can take values of 'Achieved' or 'Not Achieved' or may be missing for any reason including discontinuation from study. According to the NRI approach, all missing values will be considered as 'Not Achieved.'

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.

8.1.3 Subject Disposition

The number and percentage of subjects who are enrolled, randomized, and received at least one dose of study drug, the number of subjects who completed the study and the number of subjects who prematurely discontinued and the reason for premature discontinuation 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").

8.1.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics of the study subjects will be summarized using descriptive statistics. Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, and range for each treatment group. 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. The *P*-value will be provided to assess the comparability of the treatment groups for Part 1.

8.1.5 Prior and Concomitant 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 the ITT analysis set. No statistical test will be performed.

Concomitant medications will be summarized using the World Health Organization Drug Dictionary with frequencies and percentages for each treatment group. No statistical test will be performed.

8.1.6 Efficacy Analysis

The co-primary and ranked secondary endpoints will be analyzed separately for EU/EMA and US/FDA regulatory purposes; these endpoints are specified in Section 5.3.3 separately for each set of analyses.

8.1.6.1 Primary Efficacy Variables

The co-primary endpoints are the proportion of subjects with clinical remission per PROs (EU/EMA) and per CDAI (US/FDA) at Week 12 and proportion of subjects with endoscopic response at Week 12 for the ITT population in Part 1.

The comparison between treatment groups on the co-primary efficacy endpoints will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by Baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologics used (> 1 and ≤ 1). Both of the co-primary efficacy endpoints will be tested at two-sided significance level of 0.05. A CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. If the average daily very soft or liquid SF or average daily AP score (EU/EMA) or CDAI (US/FDA) data at Week 12 are missing, the NRI approach will be applied for the clinical remission per PROs and clinical remission per CDAI endpoints, respectively. Subjects

who discontinue prior to Week 12 for any reason will be considered as "not-achieved" for clinical remission or endoscopic response endpoints.

8.1.6.2 Secondary Efficacy Variables

A multiple testing procedure will be used to provide strong control of the type 1 error rate at alpha = 0.05 (2-sided) across analyses with respect to the co-primary endpoints, and ranked secondary endpoints as specified in Section 5.3.3. Specifically, testing will utilize a sequence of hypothesis testing for the co-primary endpoints followed by the ranked secondary endpoints, and will begin with testing co-primary endpoints using α of 0.05 (2-sided). If both co-primary endpoints achieve statistical significance, continued testing will follow a pre specified weight of α allocation between individual hypotheses as well as between families of hypotheses. The details of the testing procedure will be specified and documented in the SAP.

In general, continuous secondary efficacy variables with repeated measurements will be analyzed using a Mixed Effect Repeated Measure (MMRM) model. Continuous secondary efficacy variables which are collected at only one post-baseline visit (such as SES-CD) will be analyzed using an Analysis of Covariance (ANCOVA) model.

Categorical secondary efficacy variables will be analyzed using the CMH test controlling for stratification variables. NRI for missing data will be used for categorical secondary endpoints.

8.1.7 Safety Analyses

Safety analyses will be performed on safety analysis sets (Part 1, Part 2 and Part 3), as defined in Section 8.1.1.2. Incidence of AEs, changes in vital signs, physical examination results, and clinical laboratory data will be assessed throughout the study. ECGs will be performed at screening and at the end of each Part 1, 2, 3 of the study. AEs and laboratory data when available will be graded as described in the NCI CTCAE, and summarized accordingly.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 30 days after the last dose of the study drug for subjects who do not participate in Study M14-430, or within 30 days after the last dose of the study drug in Study M14-431 or first dose of study drug in Study M14-430 if the subject enrolls in Study M14-430, whichever comes first.

An overview of treatment-emergent AEs, including AEs leading to death, AEs leading to premature discontinuation, AEs by MedDRA preferred term and system organ class, AEs by maximum relationship to study drug, AEs by maximum severity and AEs of special interest will be summarized by number and percentage.

Changes from Baseline in continuous laboratory and vital sign parameters will be summarized by treatment group. Treatment group differences between upadacitinib and placebo groups for changes from Baseline may be analyzed using a one-way ANOVA. Vital signs and laboratory data will be described by statistical characteristics and frequency of abnormal values. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Analysis details will be specified in the SAP.

8.1.8 Pharmacokinetic and Exposure-Response Analyses

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

Population PK analyses will be performed using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The structure of the starting PK

model will be based on the PK analysis of data from previous studies. The CL/F and V/F of upadacitinib will be the PK 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 PK 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 non-linear mixed-effects modeling. The relationship between these conditional estimate 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 PK parameters with various covariates will be explored.

Relationships between upadacitinib exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for efficacy variables and/or some safety measures of interest may also be explored. The relationship between exposure (e.g., population PK model predicted average concentrations, area under the curve, trough concentrations, the individual model-predicted PK profiles, or some other appropriate measure of exposure) and drug effect will be explored. Several classes of models (e.g., linear, log-linear, exponential, maximum effect [E_{max}], sigmoid E_{max}, etc.) will be evaluated to characterize the exposure-response relationship based on observed data. Results of the PK and exposure-response analyses may be summarized in a separate report prior to regulatory filing of upadacitinib for the treatment of CD, rather than in the CSR.

Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The co-primary endpoints are the proportion of subjects with clinical remission per PROs (EU/EMA) and per CDAI (US/FDA) at Week 12 and the proportion of subjects who achieve endoscopic response at Week 12.

Sample size calculation is based on the maximum sample size needed to detect treatment difference for each of the co-primary endpoints. The assumptions used were based on the 16-week clinical and endoscopic data from the upadacitinib Phase 2 CD Study M13-740.

For EU/EMA regulatory purposes: Assuming a rate of 12% for clinical remission per PROs in the placebo group and 29% in the upadacitinib group at Week 12, a total sample size of 495 subjects randomized in a 2:1 ratio (330 subjects in the upadacitinib group and 165 subjects in the placebo group) will be adequate to detect at least a 17% treatment difference in clinical remission rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

For US/FDA regulatory purposes: Assuming a rate of 20% for clinical remission per CDAI in the placebo group and 40% in the upadacitinib group at Week 12, the same

sample size of 495 subjects will be adequate to detect at least a 20% treatment difference in clinical remission rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

Assuming an endoscopic response rate of 10% in the placebo group and 25% in the upadacitinib group at Week 12, this sample size will be adequate to detect at least a 15% treatment difference in endoscopic response rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

The objective of Part 2 is to have a sufficient number of subjects with clinical response to be re-randomized in the double-blind maintenance portion of Study M14-430. A total of 130 subjects enrolled in Part 2 would provide adequate number of subjects achieving clinical response to be re-randomized to the maintenance portion of Study M14-430.

8.3 Randomization Methods

A total of 495 subjects will be randomized in Part 1 of the study in a 2:1 ratio to upadacitinib 45 mg QD or matching placebo (330 subjects for upadacitinib 45 mg dose group and 165 for placebo group). Randomization will be stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and ≥ 15), and number of prior biologic treatments (> 1 and ≤ 1).

Subjects enroll into Part 3 from Part 2 of the study in an open-label manner. Subjects enrolling in Part 3 from Part 1 are assigned either upadacitinib 45 mg QD or upadacitinib 30 mg QD depending on the randomized treatment received in Part 1 (placebo or upadacitinib 45 mg) in a blinded fashion.

9.0 Ethics

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP and all other applicable regulatory requirements.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that

have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

In the event a state of emergency due to the COVID-19 or any pandemic leads to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and shipping investigational product and/or supplies DTP to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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 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.

Samples for exploratory research will only be collected and tested after the subject has voluntarily signed and dated the separate written consent for exploratory research, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the exploratory research, it will not impact the subject's participation in the study.

In the event a subject withdraws from the main study, optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

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

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating 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 eCRF) may serve as the source for this data point. This AE data point required for eCRF completion can be entered directly in the eCRF.

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.

During the COVID-19 or any pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Electronic Case Report Forms (eCRF)

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

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will

be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

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

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) system 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 system is available through the vendor, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

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

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO 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 ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Diary Based

The ePRO data (number of total and liquid or very soft stools, stool consistency per Bristol Stool Chart, use of medications used for endoscopy preparation, if an endoscopy was performed, AP, and general well-being) will be collected electronically via a handheld device into which the subject will record the required pieces of information on a daily basis. The electronic device will be programmed to allow 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, up until the generation, receipt and confirmation of the study archive.

Tablet Based

The ePRO data (IBDQ, CSS, EQ-5D-5L, WPAI-CD, SF-36, FACIT-F, PGI-S, and PGIC) will be collected electronically via an onsite device at visits specified in Appendix C. The electronic device will be programmed to allow data entry once per day per study subject.

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 investigator and delegated staff, will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Due to the COVID-19 or any pandemic, subject visits may be conducted via phone or video conference. PROs are eligible for completion by interview at the visits specified in Appendix C. In this situation, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with the name of the person who collected the information.

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will, throughout the study, verify that all subjects signed agreement of informed consent prior to any study-specific procedures being conducted. The study monitor will confirm that the investigator is conducting the study in compliance with the protocol, GCP and applicable regulations, and verify that the information reported in the eCRF is complete, accurate, and supported by information in source documents.

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

12.0 Use of Information

All information concerning upadacitinib 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 upadacitinib. 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 exploratory research that may be done using the samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from exploratory research from this study may be used in scientific publications or presented at medical conventions. Exploratory research

data will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator (Director of the Site in Japan) 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 (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator (Director of the Site in Japan) 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 Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for upadacitinib.
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 Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy
Protocol Date:	05 March 2021

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 Development, Immunology
		Clinical Program Development
		Clinical Pharmacology and Pharmacometrics
		Statistics
		Medical Writing

Appendix C. Study Activities

Activity	Part 1 – 12-Week Double-Blind Induction Part 2 – Open-Label Single-Arm Induction						Part 3 – Extended Treatment Period			Premature Discontinuation Visit	Unscheduled Visit[b]	30-Day Follow-Up Visit
	Screening[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24			
Informed Consent	X											
Inclusion/Exclusion[c]	X	X										
Medical/Surgical History[c]	X	X										
Prior and Concomitant Medications[c,#]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[d,+] and Vital Signs[e,#]	X	X	X	X	X	X	X	X	X	X	X	
Endoscopy[f,+] and SES-CD	X					X			X	X		
Biopsy[g,+]	X					X			X	X		
12-Lead ECG[h,+]	X					X			X	X		
Latent TB Risk Factor Assessment Form	X											
PPD Skin Test or QuantiFERON-TB Gold Test[i]	X											
Chest X-ray[j]	X											
FSH[k]	X											
HBV, HCV and HIV Screening[l]	X											
HBV Periodic Screening[m,+]						X			X			

Activity	Part 1 – 12-Week Double-Blind Induction Part 2 – Open-Label Single-Arm Induction						Part 3 – Extended Treatment Period			Premature Discontinuation Visit	Unscheduled Visit[b]	30-Day Follow-Up Visit
	Screening[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24			
C. difficile toxin	X											
Blood Chemistry and Hematology[n,o,ab,+]	X	X	X	X	X	X	X	X	X	X	X	X
hs-CRP[=]		X	X	X	X	X	X	X	X	X	X	X
Urinalysis[o,p,ab,+]	X					X			X	X		
Pregnancy Test[q,ab,+]	X	X	X	X	X	X	X	X	X	X		X
Upadacitinib Plasma Concentration[r,=]			X	X	X	X	X	X	X	X		
Stool Sample (FCP)[s,=]		X		X		X	X		X	X		
Lymphocyte Subsets[=]		X		X		X	X		X	X		
CDAI[=]		X[t]	X	X	X	X	X	X	X	X	X	
Patient Questionnaires:[#] IBDQ EQ-5D-5L WPAI SF-36 FACIT-F CSS		X		X		X			X	X		
PGI-S[#]		X	X	X	X	X			X	X	X	
PGIC[#]			X	X	X	X			X	X	X	
AE Assessment[u,#]	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing/ Administration[ab]		X		X	X	X[v]	X	X				

Activity	Part 1 – 12-Week Double-Blind Induction Part 2 – Open-Label Single-Arm Induction						Part 3 – Extended Treatment Period			Premature Discontinuation Visit	Unscheduled Visit[b]	30-Day Follow-Up Visit
	Screening[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24			
Dispense Subject Diary	X											
Subject Diary Review[w,#]		X	X	X	X	X	X	X	X	X	X	
Optional biologic drug level[x,=]	X											
Optional Pharmacogenetic[y,=]		X										
Optional Epigenetic[y,=]		X		X		X			X	X		
Optional Serum and Plasma[y,=]		X		X		X			X	X		
Optional mRNA[y,=]		X		X		X			X	X		
Optional Stool Proteomic[y,z,=]		X		X		X						
Optional Stool Microbiota[y,z,=]		X		X		X						
Optional Intestinal Biopsy[aa,=]	X					X			X	X		

CDAI = Crohn's Disease Activity Index; CSS = Crohn's Symptoms Severity Questionnaire; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Levels; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FCP = fecal calprotectin; hs-CRP = high-sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; PGIC = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; SES-CD = Simplified Endoscopic Score for Crohn's disease; SF-36 = Short Form-36; PD = premature discontinuation; WPAI = Work Productivity and Activity Impairment Questionnaire

a. The Screening Period will be a minimum of 8 days but no more than 35 days prior to Baseline Visit. Baseline Visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits.

b. Visits to retest a lab will not be considered an unscheduled visit. Unscheduled visits according to this table are for purposes when the subject is coming in for a visit for evaluation and assessment.

c. Update inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information to assure subject eligibility. All subjects need to have their average daily very soft or liquid SF and average daily AP score calculated and meeting eligibility criteria before randomization at Baseline.

d. Physical examinations are full physical examinations performed at Screening, Baseline, and Week 12; and Week 24/PD if the subject undergoes Part 3. Physical examinations at all other visits are symptom-based but should include an assessment of EIMs and presence or absence of cutaneous fistulas, as part of calculating the CDAI. During the full physical examination, all subjects will be assessed for presence and number of draining and non-draining enterocutaneous (perianal and abdominal) and rectovaginal fistulas at Baseline, Week 12, and Week 24/PD. If the assessment of presence and number of draining and non-draining fistulas were performed during Screening or the visit for endoscopy, this may be used for the respective Baseline, Week 12 or Week 24/PD visits.

e. 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).

f. Ileocolonoscopies will be used to calculate the SES-CD. The Screening ileocolonoscopy should be done during the Screening Period or within 45 days of the Baseline Visit, if video recorded. Endoscopic evaluations using SES-CD confirmed by central reader will be done at Screening. Patients who complete at least 8 weeks in Part 1 and Part 2 or at least 20 weeks in Part 3 will be required to have an endoscopy. Where COVID-19 or any pandemic affects Week 12 or Week 24 endoscopy, a ± 7-day window is permitted.

g. Biopsy may be done when performing the endoscopy. At Screening, biopsy to confirm CD diagnosis must 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. Optional intestinal biopsy samples for histopathology and biological investigations, including but not limited to, transcriptomic analyses and immunohistochemistry may be evaluated in approximately 200 subjects (intestinal biopsy substudy).

h. 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.

i. PPD skin test is to be read 48 to 72 hours after placement. Subjects with negative QuantiFERON TB Gold test and/or PPD test within 90 days of Screening will not require a repeat test (documentation must be available). In case of positive PPD/positive or repeat indeterminate IGRA testing, in the absence of active TB, the subject may participate in the study after initiation of latent TB treatment (regimen according to local practice/guidelines).

j. Chest x-ray includes posterior-anterior view and lateral view. Subjects can have a chest x-ray anytime during the study as warranted based on the opinion of the investigator. In Japan and China, a CT scan of the chest may be performed in lieu of a chest x-ray, at the investigator's discretion.

k. FSH should be tested at Screening if the female subject is ≤ 55 years of age AND has had no menses ≥ 12 months AND has no history of permanent surgical sterilization (Refer to Section 5.2.4).

l. Subjects will be tested for the presence of HBV and HCV at Screening. A positive result for HBs Ag or hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be exclusionary. For subjects who are negative for both HBs Ag and HBs Ab but are positive for HBc Ab, HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary. HIV testing will be performed at the central laboratory, unless prohibited by local regulations. The central lab will report the HIV test results directly to the sites. AbbVie will not receive results from the HIV testing and not be made aware of any positive result.

m. For Japan or countries who mandate periodic screening for HBV: subjects with positive HBs Ab and/or positive HBc Ab and a negative HBV DNA PCR test result at Screening should have HBV DNA PCR test performed at 12 and 24 weeks; in cases where recurrence of HBV DNA is observed, the subject should be discontinued from the study. This measure is not necessary in patients with history of HBV vaccination and positive HBs Ab result.

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

o. Minimum 8-hour fast for chemistry. If a subject is not able to fast, the non-fasting status will be recorded in study source documentation. Urinalysis, chemistry and hematology may be collected at other scheduled and unscheduled visits than indicated in the table in case of repeat test for toxicity management criteria or if they are warranted by the investigator.

p. Urinalysis will be completed by the central lab at the required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

q. Serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy test will be performed locally at the Baseline Visit prior to the first dose of study drug and at all subsequent visits, including the 30-day follow-up visit for all women of childbearing potential (refer to Section 5.2.4). If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. If serum pregnancy test comes back borderline, a repeat test is necessary (pregnancy is an exclusion criterion). If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study in absence of clinical suspicion of pregnancy or other pathological cause of borderline result. If a pregnancy is identified, the pregnancy must be reported to AbbVie.

r. At the Week 4 visit, PK samples should be collected prior to dosing if possible and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample should be collected at any time during the visit. At Week 16 and Week 20 visits, PK samples will not be collected from subjects in Part 3 Cohort 3, who received open-label upadacitinib in Part 2. For all other visits, PK samples should be collected at any time during the visit and the subject should follow the regular dosing schedule.

s. A stool sample will be collected at each time point indicated for FCP. For the visit that endoscopy will be conducted, stool sample should be collected prior to bowel prep. Subjects will be asked to provide a stool sample at the visit, if possible, or the site will give instructions and a stool sample supply kit.

t. Diary information collected during Screening will serve to calculate Baseline CDAI.

u. Collection of SAEs begins the day the subject signs the informed consent form.

v. Only for subjects continuing into Part 3.

w. Diary review includes a review of ePRO data (number of total and liquid or very soft stools, stool consistency per Bristol Stool Chart (Appendix F), use of medications used for endoscopy preparation, if an endoscopy was performed, AP, and general well-being).

x. During Screening, biologic drug levels may be optionally assessed at the investigator's discretion as an alternative to completing the required washout period: (1) infliximab and natalizumab: may be tested approximately 4 weeks from the last dose; (2) adalimumab, certolizumab, golimumab, or vedolizumab: may be tested approximately 6 weeks from the last dose; (3) ustekinumab: may be tested approximately 8 weeks from the last dose.

y. Only if subject provides written consent to collect the samples; if the informed consent form is not signed, no samples can be collected.

z. Optional stool samples for proteomic and microbiota analyses may be evaluated in approximately 200 subjects (fecal biomarker substudy).

aa. If subject provides written consent, intestinal biopsy samples for histology and exploratory analyses will be collected in approximately 200 subjects as a substudy; if the informed consent form is not signed, no intestinal biopsy can be collected. Biopsies will be obtained at Screening and at the Week 12 endoscopy; and at Week 24/PD, if the subject participates in Part 3.

ab. During the COVID-19 or any pandemic, when a lab test cannot be collected per protocol, the administration and dispensing of study drug should occur if the investigator feels it is safe to continue study drug based on the remote visit, at least one post-Baseline lab test is available and no longer than 6 weeks have passed since the last safety lab tests. A local laboratory can be utilized when it is not feasible to use the central laboratory.

\# Study activity that can be performed by phone/virtually within a ± 7-day window when an onsite study visit is not possible due to COVID-19 or any pandemic, if allowed by local regulations. This is applicable for all visits, except Screening and Baseline visits, which must be completed at the study site. Physical examination that requires palpation should not be performed. Patient questionnaire EQ-5D-5L is not eligible to be performed by phone/virtually.

\+ Study activity that can be performed at a local facility when an onsite study visit is not possible due to COVID-19 or any pandemic, if allowed by local regulations. This is applicable for all visits, except Screening and Baseline visits, which must be completed at the study site.

= Study activity should not be performed by phone/virtually or at a local facility, when an onsite study visit is not possible due to COVID-19 or any pandemic. Screening and Baseline visit procedures must be completed at the study site.

Appendix D. Latent TB Risk Factor Assessment Form 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

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

Appendix E. Patient Reported Outcomes Descriptions

IBDQ – Inflammatory Bowel Disease Questionnaire

The IBDQ is a disease-specific instrument composed of 32 Likert-scaled items. The total score ranges from 32 to 224 using the 7-point response options, with higher scores indicating better health-related quality of life. The IBDQ scale contains 4 component subscales: bowel symptoms, systemic symptoms, emotional function, and social function. Each subscale can be computed with total scores ranging from 10 – 70, 5 to 35, 12 to 84, and 5 to 35, respectively.[27,28]

WPAI-CD – Work Productivity and Activity Impairment Questionnaire-Crohn's Disease

The Work Productivity and Activity Index assesses the impact of the condition on work productivity losses and impairment in daily activity. WPAI has six items covering four domains: Absenteeism (work time missed), measured as the number of hours missed from work in the past 7 days due to a condition related problems. Scores are expressed as impairment percentages, adjusting for hours actually worked according to the WPAI scoring algorithm; Presenteeism (impairment at work/reduced on-the-job effectiveness), measured as the impact of the condition on productivity while at work (i.e., reduced amount or kind of work, or not as focused as usual). Responses are recorded on a 0 – 10 Likert scale (where, 0 = no effect of CD on work and 10 = severe impact of CD while at work); productivity loss (overall work impairment), measured as the sum of hours missed due to condition i.e., absenteeism and number of hours worked with impairment i.e., product of number of hours worked and presenteeism; and activity impairment (i.e., activities other than paid work like work around house, cleaning, shopping, traveling, studying), recorded and scored in same way as presenteeism. Higher numbers indicate greater impairment and less productivity.[29]

CSS – Crohn's Symptoms Severity Questionnaire

SF-36 – Short Form 36

The SF-36 questionnaire is a self-administered multi-domain scale with 36 items. Eight subscales cover a range of functioning: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The scoring yields a physical component score, a mental component summary score, and subscale scores. Higher scores represent better outcomes. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the benefit of different treatments.[30,31]

EQ-5D – European Quality of Life 5 Dimensions

The EQ-5D-5L is a standardized non-disease specific instrument for describing and valuing health-related quality of life. The EQ-5D consists of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problem, slight problem, moderate problem, severe problem or unable to do the activity. It also contains a Visual Analogue Scale (VAS). Subjects are asked to indicate the level that describes their current level of function or experience for each

dimension. As a measure of health status, it provides a descriptive profile and can be used to generate a single index value for health status, where full health is equal to 1 and death is equal to 0. The VAS records the subject's assessment of his/her own health along a vertical 20 cm line, which has health state scores between 0 and 100.[32]

FACIT-F – Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy system is a collection of quality of life (QoL) questionnaires targeted to the management of cancer and other chronic illnesses. The FACIT-F questionnaire was developed to assess fatigue associated with anemia. It consists of 13 fatigue-related questions. The responses to the 13 items on the FACIT-F questionnaire are each measured on a 4-point Likert scale. The responses to the answers are the following: (i) not at all: 0 points; (ii) a little bit: 1 point; (iii) somewhat: 2 points; (iv) quite a bit: 3 points; (v) very much: 4 points. Thus, the total score ranges from 0 to 52. High scores represent less fatigue.[33]

PGIC – Patient Global Impression of Change

The PGIC is a self-administered instrument that assesses change in the overall symptoms due to Crohn's disease. The PGIC is one item in which subjects are asked to rate overall improvement since start of the treatment. Subjects rate their change as "Very much improved," "Much improved," "Minimally improved," "No change," "Minimally worse," "Much worse" and "Very much worse."

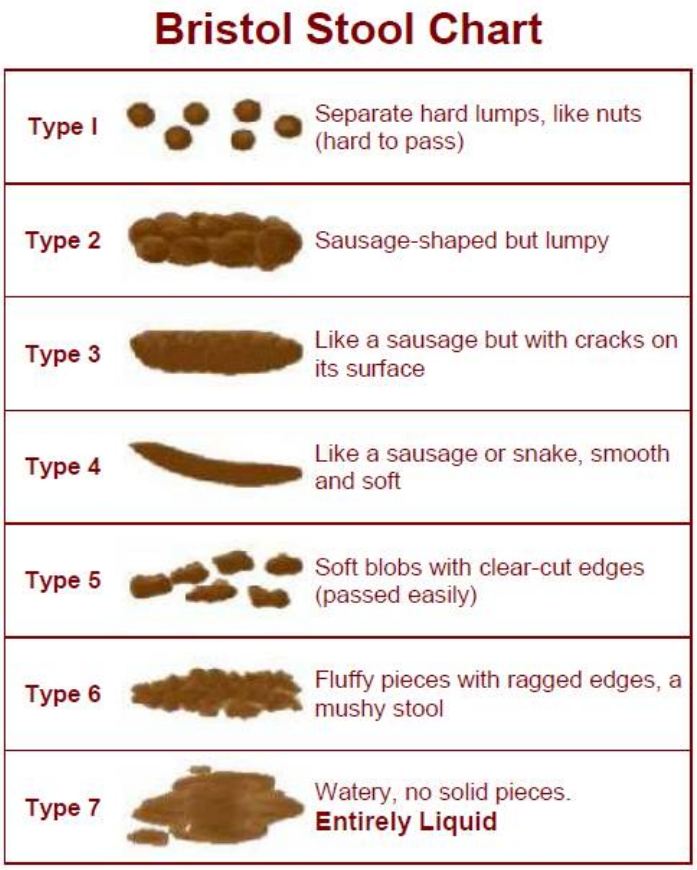
PGI-S – Patient Global Impression of Severity

The PGI-S is a self-administered instrument that assesses the severity of the overall symptoms due to Crohn's disease. The PGI-S is one item in which subjects are asked to rate overall severity of symptoms over the past week. Subjects rate their change as "Absent," "Minimal," "Mild," "Moderate," "Moderately severe," "Severe" and "Very severe."

HCRU – Health Care Resource Use

Health Care Resource use data on number of Hospitalization and surgeries will be collected through subject Administration module SAE supplemental Page.

Appendix F. Bristol Stool Chart



BSF-Scale – United Kingdom/English - Mapi.
BSF-Scale_AU1.0_eng-GBori.doc

Appendix G. Corticosteroid Taper

Beginning at Week 4, all subjects will undergo the mandatory taper schedule outlined below, in which all subjects continuing in the study will have corticosteroid discontinued no later than Week 11. For subjects entering the study on a corticosteroid dose that is in between two specific levels in taper schedule, the dose beginning at Baseline will be rounded up to the closest higher dose.

	Prednisone or Prednisolone Dose Change at Each Study Week								
Baseline Dose	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**
30 mg/day	25 mg	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg	Discontinue	0
25 mg/day	20 mg	15 mg	10 mg	7.5 mg	5 mg	2.5 mg	Discontinue	0	0
20 mg/day	15 mg	10 mg	7.5 mg	5 mg	2.5 mg	Discontinue	0	0	0
15 mg/day	10 mg	7.5 mg	5 mg	2.5 mg	Discontinue	0	0	0	0
10 mg/day	7.5 mg	5 mg	2.5 mg	Discontinue	0	0	0	0	0
7.5 mg/day	5 mg	2.5 mg	Discontinue	0	0	0	0	0	0
5 mg/day	2.5 mg	Discontinue	0	0	0	0	0	0	0
2.5 mg/day	Discontinue	0	0	0	0	0	0	0	0

	Budesonide Dose Change at Each Study Week								
Baseline Dose	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**
9 mg/day	6 mg	6 mg	3 mg	3 mg	Discontinue	0	0	0	0
6 mg/day	3 mg	3 mg	Discontinue	0	0	0	0	0	0
3 mg/day	Discontinue	0	0	0	0	0	0	0	0

	Methylprednisolone Dose Change at Each Study Week								
Baseline Dose	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**
24 mg/day	20 mg	16 mg	12 mg	8 mg	6 mg	4 mg	2 mg	Discontinue	0
20 mg/day	16 mg	12 mg	8 mg	6 mg	4 mg	2 mg	Discontinue	0	0
16 mg/day	12 mg	8 mg	6 mg	4 mg	2 mg	Discontinue	0	0	0
12 mg/day	8 mg	6 mg	4 mg	2 mg	Discontinue	0	0	0	0
8 mg/day	6 mg	4 mg	2 mg	Discontinue	0	0	0	0	0
6 mg/day	4 mg	2 mg	Discontinue	0	0	0	0	0	0
4 mg/day	2 mg	Discontinue	0	0	0	0	0	0	0
2 mg/day	Discontinue	0	0	0	0	0	0	0	0

	Hydrocortisone Dose Change at Each Study Week								
Baseline Dose	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**
120 mg/day	100 mg	80 mg	60 mg	40 mg	30 mg	20 mg	10 mg	Discontinue	0
100 mg/day	80 mg	60 mg	40 mg	30 mg	20 mg	10 mg	Discontinue	0	0
80 mg/day	60 mg	40 mg	30 mg	20 mg	10 mg	Discontinue	0	0	0
60 mg/day	40 mg	30 mg	20 mg	10 mg	Discontinue	0	0	0	0
40 mg/day	30 mg	20 mg	10 mg	Discontinue	0	0	0	0	0
30 mg/day	20 mg	10 mg	Discontinue	0	0	0	0	0	0
20 mg/day	10 mg	Discontinue	0	0	0	0	0	0	0
10 mg/day	Discontinue	0	0	0	0	0	0	0	0

Appendix H. Standard Weights

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
121.9 (48.0)		40.8 (89.9)
123.2 (48.5)		41.3 (91.0)
124.5 (49.0)		41.8 (92.1)
125.7 (49.5)		42.3 (93.3)
127.0 (50.0)		42.8 (94.4)
128.3 (50.5)		43.4 (95.6)
129.5 (51.0)		43.9 (96.8)
130.8 (51.5)		44.4 (98.0)
132.1 (52.0)	55.5 (122.4)	45.0 (99.2)
133.4 (52.5)	55.7 (122.7)	45.5 (100.4)
134.6 (53.0)	55.8 (123.1)	46.1 (101.6)
135.9 (53.5)	56.0 (123.5)	46.6 (102.8)
137.2 (54.0)	56.2 (123.9)	47.2 (104.1)
138.4 (54.5)	56.4 (124.4)	47.8 (105.3)
139.7 (55.0)	56.7 (124.9)	48.3 (106.6)
141.0 (55.5)	56.9 (125.5)	48.9 (107.9)
142.2 (56.0)	57.2 (126.1)	49.5 (109.1)
143.5 (56.5)	57.4 (126.7)	50.1 (110.4)
144.8 (57.0)	57.7 (127.3)	50.7 (111.7)
146.1 (57.5)	58.1 (128.0)	51.3 (113.0)
147.3 (58.0)	58.4 (128.7)	52.2 (115.0)
148.6 (58.5)	58.7 (129.5)	52.6 (116.0)
149.9 (59.0)	59.1 (130.3)	53.1 (117.0)
151.1 (59.5)	59.5 (131.1)	53.6 (118.3)
152.4 (60.0)	59.9 (132.0)	54.2 (119.5)
153.7 (60.5)	60.3 (132.9)	54.8 (120.8)
154.9 (61.0)	60.7 (133.8)	55.3 (122.0)
156.2 (61.5)	61.1 (134.8)	56.0 (123.5)
157.5 (62.0)	61.7 (136.0)	56.7 (125.0)
158.8 (62.5)	62.1 (137.0)	57.4 (126.5)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
160.0 (63.0)	62.6 (138.0)	58.0 (128.0)
161.3 (63.5)	63.0 (139.0)	58.7 (129.5)
162.6 (64.0)	63.5 (140.0)	59.4 (131.0)
163.8 (64.5)	64.1 (141.3)	60.1 (132.5)
165.1 (65.0)	64.6 (142.5)	60.8 (134.0)
166.4 (65.5)	65.2 (143.8)	61.4 (135.5)
167.6 (66.0)	65.8 (145.0)	62.1 (137.0)
168.9 (66.5)	66.4 (146.5)	62.8 (138.5)
170.2 (67.0)	67.1 (148.0)	63.5 (140.0)
171.5 (67.5)	67.8 (149.5)	64.2 (141.5)
172.7 (68.0)	68.5 (151.0)	64.9 (143.0)
174.0 (68.5)	69.2 (152.5)	65.5 (144.5)
175.3 (69.0)	69.8 (154.0)	66.2 (146.0)
176.5 (69.5)	70.5 (155.5)	66.9 (147.5)
177.8 (70.0)	71.2 (157.0)	67.6 (149.0)
179.1 (70.5)	71.9 (158.5)	68.3 (150.5)
180.3 (71.0)	72.6 (160.0)	68.9 (152.0)
181.6 (71.5)	73.4 (161.8)	69.6 (153.5)
182.9 (72.0)	74.1 (163.5)	70.3 (155.0)
184.2 (72.5)	75.0 (165.3)	71.2 (156.9)
185.4 (73.0)	75.7 (167.0)	71.9 (158.5)
186.7 (73.5)	76.6 (169.0)	72.6 (160.2)
188.0 (74.0)	77.5 (171.0)	73.4 (161.8)
189.2 (74.5)	78.4 (172.8)	74.1 (163.4)
190.5 (75.0)	79.1 (174.5)	74.9 (165.1)
191.8 (75.5)	80.2 (176.8)	75.6 (166.8)
193.0 (76.0)	81.2 (179.0)	76.4 (168.4)
194.3 (76.5)	82.0 (180.8)	77.2 (170.1)
195.6 (77.0)	82.9 (182.9)	77.9 (171.8)
196.9 (77.5)	83.9 (185.0)	78.7 (173.5)
198.1 (78.0)	84.9 (187.2)	79.5 (175.2)
199.4 (78.5)	85.9 (189.4)	80.3 (177.0)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Standard Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
200.7 (79.0)	86.9 (191.6)	81.0 (178.7)
201.9 (79.5)	87.9 (193.9)	81.8 (180.5)
203.2 (80.0)	89.0 (196.2)	82.6 (182.2)
204.5 (80.5)	90.0 (198.6)	*Standard height is calculated using actual height obtained at screening (without shoes) plus 1 inch or 2.5 cm
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 I. 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	

NOTE: At Baseline, subjects will be instructed on how to calculate the number of very soft and liquid stools, including a visual depiction.

Appendix J. Simple Endoscopic Score for Crohn's Disease (SES-CD[34]) Assessment

	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 =	