1.0 Title Page

Clinical Study Protocol M14-234

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

Incorporating Administrative Changes 1, 2, and 3 (Canada Only), and Amendments 0.01, 0.02, 1, 2, 3, 3.01, 4, 5, 6, and 7

AbbVie Investigational Product:	Upadacitinib (ABT-494)	
Date:	10 May 2021	
Development Phase:	2b/3	
Study Design:	Phase 2b/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study	
EudraCT Number:	2016-000641-31	
Investigators:	Multicenter. Investigator information is on file at AbbVie.	
Sponsor:	For EU Member States:* AbbVie Deutschland GmbH & Co. KG Knollstrasse 50 67061 Ludwigshafen Germany	For non-EU Member States: AbbVie Inc. 1 North Waukegan Road, AP-31-2 North Chicago, IL 60064, United States For Japan: AbbVie GK 3-1-21 Shibaura, Minato- ku, Tokyo 108-0023, Japan

Sponsor/Emergency Contact: [redacted]
200 Sydney Street
Cambridge, MA 02139
United States

Phone: [redacted]
Cell:
Fax:
Emergency 24 hour Number:
+1 973-784-6402

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

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	03 June 2016
Amendment 0.01 (US and Japan Only)	25 July 2016
Administrative Change 1 (US/Puerto Rico, Japan, and Canada)	01 August 2016
Amendment 0.02 (United Kingdom, Ireland, Austria, Belgium, Finland, Germany, Greece, Italy, Hungary, Norway, Portugal, Spain, Sweden, Czech Republic, Estonia, Latvia, Lithuania, Poland, and Romania Only)	16 September 2016
Amendment 1	29 September 2016
Administrative Change 2	21 February 2017
Amendment 2	10 October 2017
Amendment 3	03 July 2018
Amendment 3.01 (Austria, Czechia, Finland, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Spain, Sweden, and United Kingdom Only)	01 November 2018
Amendment 4	24 April 2019
Administrative Change 3 (Canada Only)	22 August 2019
Amendment 5	29 April 2020
Amendment 6	31 July 2020

The purpose of this amendment is to:

- **Apply administrative changes throughout the protocol.**

  Rationale: *Revised text to improve consistency and readability, provide clarity.*

- **Update Section 1.2 Synopsis**
  - Updated wording on the status of enrollment.

    Rationale: *Revised to be consistent with Amendment 7 revisions.*
  - Updated the Substudy 3 ranked secondary endpoints.

    Rationale: *Updated to reflect revised secondary variables.*
  - Included use of NRI-C method primary analysis.

Rationale: *clarified NRI-C approach is used for Substudy 2 and Substudy 3 primary analysis of the primary endpoint.*

- Clarified the primary ITT and Substudy 3 ITT populations.

  Rationale: *Re-grouped the Substudy 3 non-primary ITT populations in order to increase the number of subjects in each non-primary population. Renamed the Substudy 3 primary ITT population.*

- **Update Section 1.3 List of Abbreviations and Definition of Terms**
  - Added NRI-C to this section.

    Rationale: *Updated to define NRI-C*
- **Update Section 4.0 Study Objective**
  - Removed UC-related hospitalizations and UC-related surgeries in the ranked secondary endpoints. Also updated wording on the status of enrollment.

    Rationale: *Updated to reflect secondary variables updated in Section 5.3.3.2.*
- **Update Section 5.3.3.2 Secondary Variables**
  - Updated the Substudy 3 ranked secondary endpoints.

    Rationale: *To ensure the most clinically relevant endpoints are included in the type-I error-controlled endpoint testing procedure.*
- **Update Section 5.3.3.3 Additional Variables**
  - Updated the Substudy 3 additional efficacy variables Substudy 3.

    Rationale: *To update time points to be consistent with study scheduled visits; to ensure clarity of the endpoints removal of duplicate endpoint.*
- **Update Section 7.0 Protocol Deviations**
  - Updated alternate contact information**.**

    Rationale: *Updated to reflect study team changes.*
- **Update Section 8.1.1.1 Intent-to-Treat Analysis Sets**
  - Clarified the primary ITT and Substudy 3 ITT populations.

  Rationale: Re-grouped the Substudy 3 non-primary ITT populations in order to increase the number of subjects in each non-primary population. Renamed the Substudy 3 primary ITT population.

- **Update Section 8.1.3 Definition of Missing Data Imputation**
  - Added NRI-C and MMRM methods for better clarification.

    Rationale: *added NRI-C and MMRM methods to ensure clarity of statistical analysis; clarified rescue handling approaches used for Substudy 1, Substudy 2, and Substudy 3.*
- **Update Section 8.1.6.1 Primary Efficacy Variables**
  - Clarified Substudy 3 subjects included in primary efficacy.

    Rationale: *updated language for clarity.*
- **Updated Section 8.1.6.1.1 and Section 8.1.6.2 Analysis of Primary Endpoint; Secondary Efficacy Variables**
  - Clarified approach for primary analysis.

    Rationale: *clarified NRI-C approach is used for Substudy 2 and Substudy 3 primary analysis of categorical endpoints.*
- **Updated Section 8.1.7 Other Statistical Analyses of Efficacy**
  - Added Substudy 3 subgroup to analysis.

    Rationale: *added a subgroup for Substudy 3 subgroup analysis.*
- **Updated Section 8.1.8.3 Analysis of Laboratory and Vital Sign Data**
  - Clarified the analysis for continuous lab and vital sign parameters.

    Rationale: *updated language for clarity.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-234
Name of Study Drug: Upadacitinib (ABT-494)	**Phase of Development:** 2b/3
Name of Active Ingredient: Upadacitinib (ABT-494)	**Date of Protocol Synopsis:** 10 May 2021

Protocol Title:

A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis.

Objective(s):

Study M14-234 comprises 3 substudies.

The primary objective of Substudy 1 (Phase 2b induction) is to characterize the dose-response, efficacy, and safety of upadacitinib compared to placebo in inducing clinical remission defined by Adapted Mayo score (using the Mayo Scoring System for Assessment of Ulcerative Colitis Activity, excluding Physician's Global Assessment) in subjects with moderately to severely active ulcerative colitis (UC) in order to identify the induction dose of upadacitinib for further evaluation in Phase 3 studies, including Substudy 2.

At the time of this amendment, Substudy 1 has closed enrollment and all subjects have completed the induction phase.

The primary objective of Substudy 2 (Phase 3 induction) is to evaluate the efficacy and safety of upadacitinib 45 mg once daily (QD) compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC.

At the time of this amendment, Substudy 2 has closed enrollment and all subjects have completed the induction phase.

The primary objective of Substudy 3 (Phase 3 maintenance) is to evaluate the efficacy and safety of upadacitinib compared to placebo in achieving clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC who achieved clinical response (per Adapted Mayo score) following induction with upadacitinib in Study M14-234 Substudy 1 or 2 or in Study M14-675. At the time of this amendment, Substudy 3 has closed enrollment.

Investigator(s):

Multicenter.

Study Site(s):

Approximately 400 sites worldwide.

Study Population:

Males and females between 18 and 75 years of age with a diagnosis of moderately to severely active UC. Adolescent males and females 16 and 17 years of age with body weight ≥ 40 kg and meet the definition of Tanner Stage 5 will be enrolled if approved by the country or regulatory/health authority in Sub-Study 2 in addition to the adult subjects. If these approvals have not been granted, only subjects ≥ 18 years old will be enrolled. The study will consist of a mixed population: biologic-inadequate responders (bio-IR) and non-biologic-inadequate responders (non-bio-IR).

Number of Subjects to be Enrolled:

A total of approximately 844 subjects will be enrolled worldwide: 382 subjects in Substudy 1 (Phase 2b induction) and approximately 462 subjects in Substudy 2 (Phase 3 induction). For Substudy 2 the number of non-bio-IR subjects enrolled will be at least 25% and not exceed 50% of the total number of subjects enrolled. A total of approximately 750 subjects from Substudy 1, Substudy 2, and Study M14-675 who achieved response following induction will be eligible to enroll in Substudy 3 (Phase 3 maintenance).

Methodology:

This is a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled study consisting of the following substudies:

Substudy 1 is a Phase 2b dose-ranging study designed to evaluate the efficacy and safety of different oral doses of upadacitinib compared to placebo as induction therapy for 8 weeks in subjects with moderately to severely active UC.

Substudy 2 is a two-part Phase 3 dose-confirming study designed to evaluate the efficacy and safety of oral administration of upadacitinib 45 mg QD compared to placebo as induction therapy for up to 16 weeks in subjects with moderately to severely active UC.

All subjects diagnosed with moderately to severely active UC defined as an Adapted Mayo score of 5 to 9 (consisting of stool frequency subscore [SFS], rectal bleeding subscore [RBS] and endoscopy subscore) with endoscopy subscore of 2 or 3 (confirmed by a central reader) and meet other eligibility criteria will be eligible to participate in Substudies 1 and 2. The population includes subjects who have demonstrated inadequate response to, loss of response to, or intolerance to biologic therapy (biologic inadequate responders [bio-IR]) and subjects who have demonstrated inadequate response to, loss of response to, or intolerance to aminosalicylates, immunosuppressants, or corticosteroids but have not failed biologic therapy (non-bio-IR). Approximately 75% of subjects enrolled in Substudy 1 were bio-IR. The number of non-bio-IR subjects will be at least 25% enrolled and not exceed 50% enrolled in Substudy 2.

Substudy 3 is a Phase 3 study designed to evaluate the efficacy and safety of oral administration of 15 mg QD and 30 mg QD of upadacitinib compared to placebo as maintenance therapy in subjects with moderately to severely active UC who achieved clinical response following induction with upadacitinib in Study M14-234 Substudy 1 or 2, or Study M14-675.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed. These measures will only be implemented under the protocol in countries that are affected by the COVID-19 pandemic.

Substudy 1:

Subjects who consent and meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into Substudy 1 (Phase 2b 8-week induction study) and randomized in a 1:1:1:1:1 ratio to one of the five treatment groups (double-blind upadacitinib induction doses or matching placebo; 50 subjects per treatment group). The randomization will be stratified by previous biologic use, baseline corticosteroid use and baseline Adapted Mayo score (≤ 7 or > 7).

Methodology (Continued):

The following are the treatment groups for Substudy 1:

- Group 1: upadacitinib 7.5 mg QD (n = 50)
- Group 2: upadacitinib 15 mg QD (n = 50)
- Group 3: upadacitinib 30 mg QD (n = 50)
- Group 4: upadacitinib 45 mg QD (n = 50)
- Group 5: Placebo QD (n = 50)

After the 250 randomized subjects completed the 8-week induction, an analysis of efficacy and safety (selected laboratory parameters) of upadacitinib versus placebo was performed. This analysis is referred to as dose-selection analysis thereafter. Based on this analysis, one induction dose (upadacitinib 45 mg QD was identified for further evaluation in Substudy 2 and Study M14-675. The results of this analysis were reviewed and discussed with regulatory authorities, as applicable, prior to initiation of enrollment of subjects in Substudy 2 and/or Study M14-675.

During the analysis period, additional subjects (132 total) continued to be enrolled into Groups 3 and 4 of Substudy 1 (upadacitinib 30 mg QD and 45 mg QD dose groups; approximately 66 subjects per dose group). The objectives of enrolling these additional subjects are to avoid interrupting the study activities during the analysis period and to support a sufficient number of subjects with clinical response to be re-randomized into the maintenance portion in Substudy 3.

Substudy 2:

Subjects who consent and meet all of the inclusion and none of the exclusion criteria will be enrolled into Substudy 2, which consists of 2 parts: (Part 1) a randomized, double-blind, placebo-controlled 8-week induction study; (Part 2) an 8-week, open-label Extended Treatment Period for clinical non-responders from Part 1 of Substudy 2.

In Part 1, approximately 462 subjects will be enrolled. Eligible subjects will be randomized in a 2:1 ratio to one of the two treatment groups (double-blind upadacitinib 45 mg QD or matching placebo) for 8 weeks. The randomization will be stratified by bio-IR status (bio-IR vs non-bio-IR), corticosteroid use (yes or no), and Adapted Mayo score (≤ 7 or > 7) at Baseline. Within bio-IR, the randomization will be further stratified by number of prior biologic treatments (≤ 1 or > 1). Within non-bio-IR, the randomization will be further stratified by previous biologic use (yes or no).

The following are the treatment groups for Part 1 of Substudy 2:

- Group 1: Upadacitinib 45 mg QD (blinded, n = 308)
- Group 2: Placebo QD (blinded, n = 154)

Part 2 is an open-label, 8-week Extended Treatment Period for subjects who did not achieve clinical response at Week 8 in Part 1 of Substudy 2. The objectives of Part 2 are to offer upadacitinib induction treatment to placebo clinical non-responders from Part 1, and to evaluate delayed clinical response in subjects who do not initially respond to upadacitinib during Part 1. The blind from Substudy 2 Part 1 will be maintained for the duration of Study M14-234.

All eligible subjects entering Part 2 will receive open-label treatment with upadacitinib 45 mg QD for 8 additional weeks (until Week 16). Subjects who achieve clinical response at Week 8 or Week 16 will be eligible to enroll into Substudy 3. Subjects who do not achieve clinical response at Week 16 will be discontinued from the study.

Methodology (Continued):

Substudy 3:

Subjects in Substudies 1, 2, or Study M14-675 who achieved clinical response after completion of the 8-week induction treatment or subjects who achieved clinical response after completion of the Extended Treatment Period in Substudy 2 or Study M14-675 will be enrolled into Substudy 3 and treated with a blinded treatment assignment for up to 52 weeks. During the COVID-19 pandemic, Investigators should make the best effort to complete the required endoscopies per protocol. Subjects who have missed the Week 8 and/or Week 16 endoscopy when performing endoscopies are prohibited during COVID-19 pandemic will not be eligible to enter Substudy 3. The Baseline Visit of Substudy 3 is completed on the same day as the final visit in the Induction Phase (either at Week 8 or at Week 16) for subjects who are eligible.

Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and $\geq 30\%$ from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. The treatment assignment in Substudy 3 will depend on the treatment received in Substudies 1, 2, or Study M14-675, as detailed below.

Substudy 3 will have 4 cohorts:

Cohort 1: Approximately 525 subjects who achieved clinical response in Study M14-234 Substudies 1, 2 and received upadacitinib 45 mg, 30 mg or 15 mg QD, or in Study M14-675 will be re-randomized to one of the following treatment groups.

Treatment groups for Cohort 1:

- Group 1: Upadacitinib 15 mg QD
- Group 2: Upadacitinib 30 mg QD
- Group 3: Placebo QD

The eligibility of entering Cohort 1 will be decided by the treatment (placebo or upadacitinib) and dose of upadacitinib received in the induction phase.

Cohort 2: approximately 60 subjects who received double-blind placebo QD treatment for 8 weeks during Study M14-234 Substudy 1, Substudy 2 Part 1, or Study M14-675 Part 1 and achieved clinical response will continue to receive blinded placebo QD in Substudy 3.

Cohort 3: approximately 150 upadacitinib 45 mg QD induction phase non-responders who received upadacitinib 45 mg during the Extended Treatment Period in Study M14-234 (Substudy 2, Part 2) and Study M14-675 (Part 2) and achieved clinical response at Week 16 will be re-randomized and receive blinded upadacitinib 30 mg QD or upadacitinib 15 mg QD in Study M14-234 (Substudy 3).

Cohort 4: approximately 15 subjects who received double-blinded treatment of upadacitinib 7.5 mg for 8 weeks during Study M14-234 (Substudy 1) and achieved clinical response will continue to receive blinded treatment of upadacitinib 7.5 mg QD in Substudy 3.

All subjects will be provided with an electronic diary (eDiary) at Screening in Study M14-234 or Study M14-675 where they will record UC-related symptoms, use of anti-diarrheals, and use of medications for endoscopy preparation. For the assessment of the clinical endpoints, the SFS and RBS will be calculated as an average of the entries recorded into the subject's diary from the most recent consecutive 3-day period prior to each study visit.

Methodology (Continued):

Subjects will undergo a full colonoscopy with biopsy for histologic assessment during Screening with local investigator assessment for Mayo endoscopic subscore for initial eligibility assessment, confirmed by a central reader prior to randomization. At end of treatment (Week 8 in Substudy 1, Substudy 2 Part 1, or Study M14-675 Part 1); Week 44 in Substudy 3 (for subjects entering from Substudy 1), or Week 52/PD in Substudy 3 (for all subjects entering from Substudy 2 and Study M14-675), a full colonoscopy or flexible sigmoidoscopy, depending on the extent of disease at Screening, will be performed.

For subjects in Substudy 2 Part 2 or Study M14-675 Part 2, an endoscopy will be performed at Week 16. A flexible rectosigmoidoscopy is recommended at Week 16, however, the use of flexible rectosigmoidoscopy or colonoscopy will be based on the investigator's discretion per local practice.

The endoscopic subscore result from the central reader during the Screening Period will be used to evaluate the eligibility of a subject to enroll in the study and for all efficacy assessments at Week 8 of Substudy 1 and Substudy 2 Part 1, Week 16 of Substudy 2 Part 2 and Week 44 (for subjects that enter from Substudy 1 prior to amendment approval) or Week 52 of Substudy 3 (for subjects that enter from Substudy 2 or Study M14-675).

However, for re-randomization into Substudy 3, the endoscopic subscore at Week 8 (Study M14-234 Substudy 1, Substudy 2 Part 1 or Study M14-675 Part 1) or Week 16 (Substudy 2 Part 2 or Study M14-675 Part 2) based on the local reader's assessment will be used to determine clinical response status compared to the baseline assessment of the central reader for enrollment into Substudy 3.

In addition to the Mayo endoscopic subscore, the central reader will assess the endoscopy findings using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scoring system for additional exploratory analyses. Blood samples will be collected for hs-CRP, upadacitinib plasma concentrations and other biomarker analyses. In addition, stool samples for fecal calprotectin will be collected. The stool samples should be taken before starting bowel preparations for scheduled endoscopies.

Electronic patient reported outcomes (ePRO) instruments: Subjects will be asked to fill out the Inflammatory Bowel Disease Questionnaire (IBDQ), Work Productivity and Activity Impairment (WPAI), European Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L), Short Form 36 Item (SF-36), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Ulcerative Colitis Symptoms Questionnaire (UC-SQ; only in select sites during Substudy 1, but all subjects will complete this questionnaire during Substudy 2 and Study M14-675) and Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) at some sites will be collected at specific visits throughout all three substudies.

Washout Period:

Subjects, who have been taking exclusionary medications prior to screening must complete medication washout. The duration is based on the excluded medication as described in the protocol. However, for subjects who have discontinued infliximab, certolizumab, adalimumab, golimumab, vedolizumab, natalizumab, ustekinumab, 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. Protocol-related adverse events should be reviewed and subjects must complete the washout prior to the Baseline Visit.

Methodology (Continued):

Concomitant UC-Related Medications (Oral Corticosteroids, Antibiotics, Aminosalicylates, and/or Methotrexate):

All UC-related concomitant medications should be kept on stable doses in Substudy 1 and Substudy 2 Parts 1 and 2.

For Substudy 3, at baseline (Week 8 or Week 16 of Study M14-234 Substudy 1, Substudy 2, and Study M14-675) subjects who are taking corticosteroid therapy will have their corticosteroid therapy tapered according to a proposed tapering schedule. All subjects receiving UC-related antibiotics may discontinue treatment starting at Week 0 of Substudy 3 at the discretion of the investigator. All subjects receiving stable dose of UC-related antibiotics (those subjects who did not discontinue), aminosalicylates, or MTX at Week 0 will maintain their concomitant treatments and respective doses through the end of the study. Dose may be decreased or terminated in the event of moderate to severe treatment related toxicity (e.g., leukopenia or elevated liver enzymes) in the opinion of the investigator.

Rescue Therapy:

At or after Week 4 in Substudy 3, subjects who demonstrate loss of response and require medical treatment but have not yet met the criteria to enter Study M14-533 Cohort 1, may receive rescue therapy. Rescue therapy should not be withheld even if subject does not meet the criteria for loss of response or before 4 weeks after entering Substudy 3 if in the opinion of the investigator, failure to prescribe them would compromise the subject's safety. Rescue therapy may be provided in the form of initiation or increased dosage, at the investigator's discretion, of any allowed UC-related medications to treat new or worsening UC symptoms. The allowed UC-related medications are locally acting, oral, or intravenous corticosteroids, aminosalicylates, MTX or UC-related antibiotics.

Diagnosis and Main Criteria for Inclusion/Exclusion:

The following Inclusion/Exclusion criteria are for subjects enrolled in both Substudies 1 and 2.

Main Inclusion:

1. Male or female between 16 and 75 years of age at Baseline.

   Subjects at 16 and 17 years of age will only be enrolled if approved by the country or regulatory/health authority and must weigh ≥ 40 kg and meet the definition of Tanner Stage 5 (refer to Appendix J) at the Screening Visit. If these approvals have not been granted, only subjects ≥ 18 years old will be enrolled.
2. Diagnosis of UC for 90 days or greater prior to Baseline, confirmed by colonoscopy during the Screening Period, with exclusion of current infection, colonic dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the investigator, must be available.
3. Active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central reader).
4. Demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments including, oral aminosalicylates, corticosteroids, immunosuppressants and/or biologic therapies, in the opinion of the investigator, as defined below

   Note: An inadequate response, loss of response, or intolerance to Oral Aminosalicylates will NOT count towards eligibility for the following countries: Austria, Czechia, Finland, France, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Spain, Sweden and United Kingdom.

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

Main Inclusion (Continued):

- Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide)
  - Signs and symptoms of persistently active disease, in the opinion of the investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide.
- Corticosteroids
  - Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥ 40 mg/day orally for at least 3 weeks or intravenously for 1 week, ***OR***
  - Unable to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease, ***OR***
  - Signs and symptoms of persistently active disease during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone, ***OR***
  - Unable to taper oral budesonide to at or below 6 mg/day without recurrent active disease, ***OR***
  - History of intolerance to corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection).
- Immunosuppressants
  - Signs and symptoms of persistently active disease despite a history of at least one 90 day regimen of oral azathioprine (≥ 1.5 mg/kg/day; for subjects in Japan, China, and Taiwan only: ≥ 1.0 mg/kg/day), 6-mercaptopurine (6-MP) (≥ 1 mg/kg/day; [for subjects in Japan, China, and Taiwan only: ≥ 0.6 mg/kg/day, rounded to the nearest available tablet of half tablet formulation] or a documented 6-thioguanine nucleotide [6-TGN] level of 230 – 450 pmol/8 × 10^8 red blood cell count [RBC] or higher on the current dosing regimen), injectable MTX (≥ 15 mg/week subcutaneous [SC] or intramuscular), or tacrolimus (for subjects in Japan and Taiwan only: documented trough level of 5 – 10 ng/mL), OR
  - History of intolerance to at least one immunosuppressant (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection)

    Note: Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study unless these subjects were previously treated with aminosalicylates, corticosteroids or immunosuppressants (azathioprine or 6-MP) and have inadequate response to, loss of response to or intolerance to the therapy as defined above.
- Biologic Agents for UC

  Signs and symptoms of persistently active disease despite a history of any of the following:
  - at least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at 0, 2, and 6 weeks),
  - at least one 4-week induction regimen of adalimumab (one 160 mg subcutaenous [SC] dose followed by one 80 mg SC dose [or one 80 mg SC dose in countries where this dosing regimen is allowed] followed by one 40 mg SC dose at least 2 weeks apart),

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

Main Inclusion (Continued):

- at least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart),
- at least one 6-week induction regimen of vedolizumab (300 mg IV at 0, 2, and 6 weeks),
- at least one induction regimen of ustekinumab, a single IV dose using weight-based dosing (260 mg for subjects with body weight ≤ 55 kg; 390 mg for subjects with body weight > 55 kg to ≤ 85 kg; 520 mg for subjects with body weight > 85 kg **OR**
- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), **OR**
- History of intolerance to at least one biologic agent (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

Note: Non-bio-IR subjects who have received a prior biologic for up to 1 year may be enrolled, however, subjects must have discontinued the biologic for reasons other than inadequate response or intolerance (e.g., change of insurance, well controlled disease), and must meet the criteria for inadequate response, loss of response or intolerance to aminosalicylates, corticorsteroids and/or immunosuppressants as defined above.

5. Female subjects of childbearing potential (refer to Section 5.2.4), must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Baseline Visit prior to study drug dosing.
6. If female, subject must meet the contraception criteria as stated in Section 5.2.4 of this protocol.

Main Exclusion:

1. Subject with current diagnosis of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the Screening endoscopy.
4. Received cyclosporine, tacrolimus, mycophenolate mofetil, or thalidomide within 30 days prior to Baseline.
5. Subject who received azathioprine or 6-mercaptopurine within 10 days of Baseline.
6. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
7. Subject with previous exposure to JAK inhibitor (e.g., tofacitinib, baricitinib, filgotinib, upadacitinib).
8. Screening laboratory and other analyses show any of the following abnormal results:
   - Serum Aspartate Transaminase (AST) or Alanine Transaminase (ALT) > 2 × upper limit of normal (ULN);
   - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 mL/min/1.73 m^2;
   - Total White Blood Cell (WBC) count < 2500/µL;
   - Absolute neutrophil count (ANC) < 1,200/µL;
   - Platelet count < 100,000/µL;
   - Absolute lymphocytes count < 750/µL;
   - Hemoglobin < 9 g/dL.

Investigational Product(s):	Upadacitinib (ABT-494)
Double-Blind Induction Doses – Phase 2b (Substudy 1):	Upadacitinib 7.5 mg QD Upadacitinib 15 mg QD Upadacitinib 30 mg QD Upadacitinib 45 mg QD
Double-Blind Induction Doses – Phase 3 (Substudy 2 – Part 1):	Upadacitinib 45 mg QD
Open-Label Induction Doses – Phase 3 (Substudy 2 – Part 2):	Upadacitinib 45 mg QD
Double-Blind Maintenance Doses – Phase 3 (Substudy 3)	Upadacitinib 7.5 mg QD Upadacitinib 15 mg QD Upadacitinib 30 mg QD
Mode of Administration:	Oral
Reference Therapy:	Matching Placebo
Dose(s):	N/A
Mode of Administration:	Oral
Duration of Treatment: 8 weeks to 16 weeks (as applicable) induction and 44 to 52 weeks maintenance for a total of up to 68 weeks	

Criteria for Evaluation:

Efficacy:

Primary Endpoints:

The primary endpoint for Phase 2b Induction (Substudy 1) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (defined as SFS ≤ 1, RBS of 0, and endoscopic subscore ≤ 1) at Week 8. The primary endpoint for Phase 3 induction (Substudy 2) is the proportion of subjects who achieve clinical remission per Adapted Mayo score, defined as SFS ≤ 1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤ 1 at Week 8. *Note:* in Substudy 2, evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

The primary endpoint for Phase 3 maintenance (Substudy 3) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (definition same as definition in Substudy 2) at Week 52.

Substudy 2 Ranked Secondary Endpoints:

1. Proportion of subjects with endoscopic improvement at Week 8
2. Proportion of subjects with endoscopic remission at Week 8
3. Proportion of subjects achieving clinical response per Adapted Mayo Score at Week 8
4. Proportion of subjects achieving clinical response per Partial Adapted Mayo score (defined as decrease from Baseline ≥ 1 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at Week 2
5. Proportion of subjects achieving histologic-endoscopic mucosal improvement at Week 8
6. Proportion of subjects who reported no bowel urgency at Week 8

Criteria for Evaluation (Continued):

Efficacy (Continued):

7. Proportion of subjects who reported no abdominal pain at Week 8
8. Proportion of subjects who achieved histologic improvement at Week 8
9. Change from Baseline in IBDQ total score at Week 8
10. Proportion of subjects with mucosal healing at Week 8
11. Change from Baseline in FACIT-F score at Week 8

Substudy 3 Ranked Secondary Endpoints:

1. Proportion of subjects with endoscopic improvement at Week 52
2. Proportion of subjects who maintain clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in Study M14-234 (Substudy 1 or 2) or Study M14-675
3. Proportion of subjects who achieved clinical remission at Week 52 per adapted Mayo score and were corticosteroid free for ≥ 90 days among subjects in clinical remission in the end of the induction treatment in Study M14-234 (Substudy 1 or 2) or Study M14-675
4. Proportion of subjects with endoscopic improvement at Week 52 among subjects with endoscopic improvement in Study M14-234 (Substudy 1 or 2) or Study M14-675
5. Proportion of subjects with endoscopic remission at Week 52
6. Proportion of subjects maintain clinical response per Adapted Mayo score at Week 52
7. Proportion of subjects with histologic-endoscopic mucosal improvement at Week 52
8. Change from Baseline in IBDQ total score at Week 52
9. Proportion of subjects with mucosal healing at Week 52
10. Proportion of subjects who reported no bowel urgency at Week 52
11. Proportion of subjects who reported no abdominal pain at Week 52
12. Change from Baseline in FACIT-F score at Week 52

Pharmacokinetic:

Blood samples will be collected for measurement of upadacitinib plasma concentration at the following times:

Substudy 1: Week 2, Week 4, Week 6, and Week 8/Premature Discontinuation (PD)

Substudy 2 Part 1: Week 2, Week 6, and Week 8/Premature Discontinuation (PD)

Substudy 3: Week 36, and Week 52/PD

Safety:

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

Criteria for Evaluation (Continued):

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, including pharmacogenetic, epigenetic, transcriptomic, proteomic and targeted investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites or lipids.

Statistical Methods:

Efficacy:

For Substudy 1 (Phase 2b portion of the study), a total of 250 subjects will be equally allocated to four upadacitinib treatment groups and the placebo group, representing a randomization ratio of 1:1:1:1:1.

The dose-response relationships using the most significant model in Multiple Comparison Procedure – Modeling (MCP-Mod) among the 4 upadacitinib treatment groups and placebo group will be characterized for the primary endpoint clinical remission per Adapted Mayo score at Week 8.

For Substudy 2, a total of 462 subjects will be allocated to upadacitinib treatment group or placebo in a randomization ratio of 2:1.

For both Substudies 1 and 2, efficacy analysis will be based on intent-to-treat (ITT) analysis set. The ITT analysis set for Substudy 1 includes all randomized subjects who received at least one dose of study drug from Substudy 1 (denoted as ITT1A) at the time of dose-selection analysis. The ITT analysis set that includes all ITT1A subjects, plus all the additional subjects who were randomized to upadacitinib 30 mg QD and 45 mg QD groups during the dose-selection period is denoted as ITT1B. ITT1A is the primary analysis set of Substudy 1. Primary analysis and ranked secondary analysis of Substudy 1 will be repeated using ITT1B. The comparisons between treatment groups for the primary efficacy endpoint will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by previous biologic use, baseline corticosteroid use and baseline Adapted Mayo score (≤ 7 and > 7). The Non-responder imputation (NRI) method, where subjects with missing data at scheduled assessment visits will be considered as "not achieved" for the clinical remission, will be used for primary analysis.

The ITT analysis set for Substudy 2 includes all randomized subjects who received at least one dose of study drug from Substudy 2 Part 1 (denoted as ITT2A). The ITT analysis set that includes all subjects who received the open label upadacitinib induction dose of 45 mg QD from Substudy 2 Part 2 is denoted as ITT2B. ITT2A is the primary analysis set of Substudy 2. Primary analysis and ranked secondary analysis of Substudy 2 will be repeated using ITT2B. The comparisons between treatment groups for the primary efficacy endpoint will be performed using the Cochran-Mantel-Haenszel (CMH) test and the randomization will be stratified by bio-IR status (bio-IR vs non-bio-IR), corticosteroid use (yes or no) and Adapted Mayo score (≤ 7 or > 7) at Baseline. Within bio-IR, the randomization will be further stratified by number of prior biologic treatments (≤ 1 or > 1). Within non-bio-IR, the randomization will be further stratified by a previous biologic use (yes or no). Non-responder imputation incorporating multiple imputation to handle COVID-19 (NRI-C) method will be used for primary analysis.

For Substudy 3, efficacy analyses will be based on the ITT analysis set.

Statistical Methods (Continued):

Efficacy (Continued):

A database lock and unblinded analysis will be conducted for the purpose of regulatory submission after the first 450 subjects in Substudy 3 Cohort 1 who were upadacitinib 45 mg QD induction responders have completed the maintenance study (i.e., completed Week 52 or prematurely discontinued prior to Week 52). This is the only and final analysis for the 52-week efficacy analyses. AbbVie study team will be unblinded to the treatment assignment, study sites and subjects will remain blinded until all subjects complete the maintenance study. If there are additional subjects in any cohort who have not completed the maintenance study at the time of database lock, they will be kept on the same blinded treatment until study completion. Once all subjects have completed the maintenance study, the data collected from these subjects will be used to update the safety analysis only.

For Substudy 3, the following ITT analysis sets are defined:

- ITT3: All subjects who received at least 1 dose of study drug in the Substudy 3.
- ITT3_A: The subset of ITT3 who were the first 450 upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1. The ITT3_A is the primary analysis population in Cohort 1 for efficacy endpoints.
- ITT3_B: The subset of ITT3 in Cohort 3 who were upadacitinib 45 mg QD 16-week induction responders.
- ITT3_C: The subset of ITT3 who were enrolled under the original protocol, Amendment 1 or 2 for 44-week maintenance treatment period.
- ITT3_D: The subset of ITT3 who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1.
- ITT3_E: The subset of ITT3 who were placebo, upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period.

Primary analysis and secondary analyses of Substudy 3 will be performed for ITT3_A, ITT3_B, ITT3_C and ITT3_E.

The comparison between treatment groups in ITT3_A population for the primary efficacy endpoint will be performed using the CMH test and will be stratified by previous bio-IR status (yes or no), clinical remission status at Week 0 (yes or no), and corticosteroid use at Week 0 (yes or no). Non-responder imputation incorporating multiple imputation to handle COVID-19 (NRI-C) method will be used for the primary analysis.

Additional analyses are outlined in the protocol.

Pharmacokinetic:

Individual plasma concentrations of upadacitinib will be tabulated and summarized. 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 (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

Statistical Methods (Continued):

Safety:

Safety analyses will be carried out using the safety analysis set in Substudies 1 to 3, which includes all subjects who receive at least one dose of study medication in each portion of the study, respectively. Incidence of adverse events, changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed. Treatment-emergent adverse events will be tabulated by system organ class and by MedDRA preferred term for each treatment group for each Substudy and over the entire study. Mean change from Baseline for laboratory and vital signs data will be summarized.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-mercaptopurine
6-TGN	6-thioguanine
AD	Atopic dermatitis
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
AUC	Area under the plasma concentration-time curve
AZA	Azathioprine
ATEMS	AbbVie Temperature Excursion Management System
BCG	Bacille Calmette-Guérin
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood Urea Nitrogen
CAC	Cardiovascular Adjudication Committee
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CD4, CD8	Cluster of Differentiation
CFR	Code of Federal Regulations
CGC	Common Gamma-Chain
CI	Confidence Interval
CL/F	Oral Clearance
C_{max}	Maximum Observed Plasma Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COVID-19	Coronavirus Disease - 2019
CPK	Creatine Phosphokinase
CR	Clinical Remission

CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
C_{min}	Minimum Plasma Concentration During a Dosing Interval
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-Ray
CYP3A	Cytochrome P450 3A
DMARD	Disease-Modifying Anti-Rheumatic Drug
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DTP	Direct-to-patient
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIMs	Extra-Intestinal Manifestations
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Levels
ER	Extended Release
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	US Food and Drug Administration
FSH	Follicule-stimulating Hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
gp130	Glycoprotein 130
GPRD	Global Pharmaceutical Research and Development
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCRU	Health Care Resource Utilization
HCV	Hepatitis C Virus

HCV Ab	Hepatitis C Virus Antibody
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HIV Ab	Anti-HIV antibody
HCRU	Health Care Resource Utilization
hs-CRP	High-Sensitivity C-Reactive Protein
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IC	Indeterminate Colitis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IGRA	Interferon-Gamma Release Assay
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenously
JAK	Janus Activated Kinase
LDL-C	Low Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Event
MCP-Mod	Multiple Comparison Procedure – Modeling
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MED	Minimum Effective Dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Repeated Measure

MTX	Methotrexate
NCI	National Cancer Institute
NK	Natural Killer Cells
NKT	Natural Killer T-Cells
NOAEL	No Observable Adverse Effect Level
NMSC	Nonmelanoma Skin Cancer
NRI	Non-Responder Imputation
NRI-C	Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC	Observed Cases
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PD	Premature Discontinuation
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PPD	Purified Protein Derivative
PRO	Patient Reported Outcomes
PsA	Psoriatic arthritis
QTcF	QT Interval Corrected for Heart Rate by Fridericia's Correction Formula
RA	Rheumatoid Arthritis
RAVE®	EDC System from Medidata
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
RBS	Rectal Bleeding Subscore
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short Form 36
SFS	Stool Frequency Subscore
SOC	System Organ Class
STAT	Signal Transduction Activators of Transcription

SUSAR	Suspected Unexpected Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition
UC	Ulcerative Colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
UC-SQ	Ulcerative Colitis Symptoms Questionnaire
ULN	Upper Limit of Normal
US	United States
V/F	Volume of Distribution
VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization
WPAI	Work Productivity and Impairment Questionnaire

Definition of Terms

Bio-IR	Biologic inadequate responders: inadequate response, loss of response, or intolerance to biologic therapy
Non-bio-IR	Non-biologic-inadequate responders: inadequate response, loss of response, or intolerance to conventional therapy but have not failed biologic therapy

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). It is postulated that UC is caused by unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals.[1] UC is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of mainly the mucosal and occasionally submucosal intestinal layers. The highest annual incidence of UC was 24.3 per 100,000 person-years in Europe, 6.3 per 100,000 person-years in Asia and the Middle East, and 19.2 per 100,000 person-years in North America, with a prevalence of 505 cases per 100,000 persons in Europe and 249 cases per 100,000 persons in North America.[2] The burden of UC on the healthcare system is profound, accounting for nearly 500,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone.[3]

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

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

The aim of medical treatment in UC is to control inflammation and reduce symptoms. Available pharmaceutical therapies are limited, do not always completely abate the inflammatory process, and may have significant adverse effects. Therapies for mild to moderate active UC include 5-aminosalicylic acid derivatives and immunosuppressants.

Corticosteroids are used in patients with more severe symptoms but are not useful for longer term therapy.[6] The frequency and severity of corticosteroid toxicities are significant, including infections, emotional and psychiatric disturbances, skin injury, and metabolic bone disease. Corticosteroids are not effective for the maintenance of remission and the UC practice guidelines from the American College of Gastroenterology recommend against chronic steroid treatment.[7] Patients with moderate to severe symptoms may derive some benefits from immunomodulatory agents (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]); however, the use of these agents is limited as induction treatment due to a slow onset of action (3 to 6 months) and as maintenance therapy due to adverse events (AEs), including bone marrow suppression, infections, hepatotoxicity, pancreatitis, and malignancies.[7,8] Despite these therapies, approximately 15% of UC patients experience a severe clinical course, and 30% of these patients require removal of the colon/rectum, to eliminate the source of the inflammatory process, although accompanied by significant morbidity.[9,10]

Biological agents targeting specific immunological pathways have been evaluated for their therapeutic effect in treating patients with UC. Anti-tumor necrosis factor (TNF) agents were the first biologics to be used for IBD. Infliximab, adalimumab, and golimumab are successfully being used for the treatment of UC. Vedolizumab, an anti-adhesion therapy, has been approved for the treatment of IBD.

Anti-TNF therapies are an effective treatment for patients who are steroid refractory or steroid dependent, who had inadequate response to a thiopurine, or who are intolerant to these medications. Potential risks with anti-TNF therapies include infusion or injection site reactions, serious infections, lymphoma, heart failure, lupus-like syndromes, and demyelinating conditions.[11] Despite the beneficial results achieved with the available biologic agents, only 17% to 45% of patients who receive them are able to achieve clinical remission.[12-15] Thus, there remains a clear medical need for additional therapeutic options in UC for patients with inadequate response to or intolerance to conventional therapies and biologic therapies.

Rationale for Development of a JAK Inhibitor in UC

The Janus kinases or JAKs are a family of intracellular tyrosine kinases that function as dimers in the signaling process of many cytokine receptors. The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases. Targeting the Janus activated kinase (JAK) signaling pathway for autoimmune diseases is supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. The activation of JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders.[16]

Tofacitinib is an oral JAK inhibitor that inhibits JAK1, JAK2 and JAK3 with high in vitro functional specificity for kinases 1 and 3. In completed Phase 3 studies in patients with moderately to severely active UC, tofacitinib was more effective than placebo as induction and maintenance therapy.[17]

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 counts, serum creatinine, total cholesterol, high density liporprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and liver transaminases (alanine transaminase [ALT], aspartate transaminase [AST]) and creatine phosphokinase (CPK).[18,19]

Upadacitinib is a novel selective Janus kinase (JAK) 1 inhibitor. JAK1 inhibition blocks the signaling of many important pro-inflammatory cytokines, including interleukin (IL)-2, IL-6, IL-7, and IL-15, which are known contributors to inflammatory disorders. Through modulation of these proinflammatory cytokine pathways, upadacitinib offers the potential for effective treatment of inflammatory or autoimmune disorders such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), giant cell arteritis (GCA), Takayasu arteritis, polyarticular course juvenile idiopathic arthritis (pcJIA), Crohn's disease (CD), UC and atopic dermatitis (AD). The clinical hypothesis is that,

based on the differentiated selectivity profile for JAK inhibition, upadacitinib could demonstrate an improved benefit/risk profile compared to other less selective JAK inhibitors or other therapeutic strategies for patients with inflammatory diseases.

To date, upadacitinib has been investigated in 22 Phase 1 studies with healthy volunteers (one of which also employed a substudy in subjects with mild to moderate RA), and multiple Phase 2 or Phase 3 studies for indications of RA, CD, AD, PsA and UC. Upadacitinib has been shown to be effective in the treatment of the indicated medical conditions based on the data available from the various studies. Safety results across the studies showed that upadacitinib was well tolerated and the types and frequencies of AEs were consistent with subjects with the medical conditions receiving immunomodulatory therapy. Many of the safety findings are expected for the class products with JAK inhibition, such as infections, increase in LDL-C and HDL-C, and asymptomatic and transient CPK elevation.

Upadacitinib has been evaluated in Phase 2b dose ranging placebo-controlled study in subjects with moderately to severely active UC with a history of inadequate response to or intolerant to immunosuppressants, corticosteroids or biologic therapies (Study M14-234 Substudy 1). At the time of this amendment, Phase 2b interim results from this Study M14-234 Substudy 1 Part 1 became available. The primary objective of demonstrating statistically significant dose-response relationship of upadacitinib compared to placebo for the primary endpoint and all ranked secondary endpoints was met, with the highest rates observed in the 45 mg once daily (QD) treatment group for both clinical and endoscopic endpoints. Upadacitinib was generally safe and well tolerated. No new safety concerns were identified compared to what has been observed in studies of upadacitinib in other disease indications.

A detailed discussion of the preclinical toxicology, metabolism, pharmacology and safety experience with upadacitinib can be found in the current Investigator's Brochure.[20]

3.1 Differences Statement

This Phase 2b/3 study differs from other upadacitinib studies as it is the first to evaluate the efficacy, safety and pharmacokinetics of upadacitinib in subjects with UC.

3.2 Benefits and Risks

Despite the availability of various UC therapies, including biologic therapies such as anti-TNFs, many patients still do not respond adequately to these treatments, or gradually lose response over time. Thus, there remains a clear medical need for additional therapeutic options in UC for patients with inadequate response to, loss of response to, or intolerance to conventional therapies and biologic therapies.

Clinical efficacy of JAK inhibition has been demonstrated in the treatment of UC. Tofacitinib is recently approved for the treatment of UC.[21] However, the non-selectivity of tofacitinib targeting JAK1, JAK2 and JAK3 has been associated with a number of safety issues.[19,22-23]

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 non-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. 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.

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. Male trial participants are therefore not required to use contraception when participating in upadacitinib clinical trials.

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.

We propose to initiate a Phase 2b/3 study in UC subjects with multiple doses of upadacitinib based on the following supportive findings: 1) demonstrated improved potency of upadacitinib versus tofacitinib in preclinical models of inflammation; 2) confirmed JAK1 selectivity of upadacitinib in both preclinical and clinical settings; 3) acceptable preclinical toxicological findings in chronic toxicity studies in two species; 4) acceptable safety and tolerability profile of upadacitinib in single ascending dose and multiple ascending dose studies in healthy volunteers; 5) evidence that JAK inhibition in inflammatory bowel disease results in clinical and endoscopic improvement; and 6) evidence of efficacy and safety in a different inflammatory disease (rheumatoid arthritis). The current Phase 2b/3 Study M14-234 will assess the benefit to risk profile of upadacitinib in subjects with moderately to severely active UC who have had an inadequate response or intolerance to oral aminosalicylates, immunosuppressants, corticosteroids, and/or biologic therapies.

As presented above, at the time of this amendment, the completed Phase 2b dose ranging part of this study (Study M14-234 Substudy 1) has demonstrated superior efficacy of upadacitinib with an acceptable safety profile compared to placebo in subjects with

moderately to severely active UC. The benefit-risk profile of upadacitinib in Substudy 1 of this study supports further evaluation of upadacitinib in Substudies 2 and 3 for subjects with UC.[24]

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.

3.3 Safety Evaluations

Safety will be assessed by AE monitoring, physical examination, vital signs, ECG, imaging and clinical laboratory testing during the study. Laboratory assessments will include hematologic parameters, chemistry, liver function tests, and lipid parameters.

4.0 Study Objective

Study M14-234 comprises 3 substudies.

The objective of Substudy 1 (Phase 2b induction) was to characterize the dose-response, efficacy, and safety of upadacitinib compared to placebo in inducing clinical remission per Adapted Mayo score (using the Mayo Scoring System for Assessment of Ulcerative Colitis Activity, excluding Physician's Global Assessment [PGA]) in subjects with moderately to severely active UC in order to identify the induction dose of upadacitinib for further evaluation in Phase 3 studies including Substudy 2.

The population in Substudy 1 included subjects who had demonstrated inadequate response, loss of response, or intolerance to biologic therapy (biologic inadequate responders [bio-IR]) and subjects who had demonstrated inadequate response to, loss of response to, or intolerance to conventional therapy but had not failed biologic therapy (non-bio-IR). Approximately 75% of subjects were bio-IR and 25% of subjects were non-bio-IR in Substudy 1. At the time of this amendment, Substudy 1 has closed and all subjects have completed the induction phase.

Subjects in Substudy 1 who did not achieve clinical response after completion of the 8-week induction treatment had the option to enroll into a separate AbbVie Study, Study M14-533, a Phase 3 multicenter, long-term extension study.

The primary objective of Substudy 2 (Phase 3 induction) is to evaluate the efficacy and safety of upadacitinib 45 mg QD compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC who are bio-IR or non-bio-IR.

The secondary objectives of Substudy 2 are to evaluate the efficacy of upadacitinib 45 mg QD comparing with placebo in ranked secondary endpoints of achieving endoscopic improvement, endoscopic remission, clinical response per Adapted Mayo Score, clinical response per Partial Adapted Mayo score, histologic-endoscopic mucosal improvement, no bowel urgency, no abdominal pain, histologic improvement, mucosal healing, and change in IBDQ total score and FACIT-F score.

Substudy 2 will allow enrollment of up to 30% of enrolled bio-IR subjects who have failed 3 or more biologics. Among non-bio-IR subjects, subjects who have used a biologic up to 1 year and have discontinued for reasons other than inadequate response, loss of response, or intolerance (e.g., change of insurance/reimbursement, well-controlled disease, etc.) may be enrolled but must meet other criteria for inadequate response, loss of response, or intolerance to aminosalicylates, corticosteroids, or immunosuppressants as defined in the protocol. The study will allow for enrollment of up to 20% enrolled non-bio-IR subjects who could also have previous use of a biologic therapy but discontinued based on reasons other than inadequate response, loss of response, or intolerance. Substudy 2 will also evaluate the efficacy of an additional 8-week upadacitinib 45 mg QD treatment in subjects who did not achieve clinical response in the initial 8-week induction phase. At the time of this amendment, Substudy 2 has closed and all subjects have completed the induction phase.

The primary objective of Substudy 3 (Phase 3 maintenance) is to evaluate the efficacy and safety of upadacitinib 30 mg QD and 15 mg QD compared to placebo in achieving clinical

remission (per Adapted Mayo score) in subjects with moderately to severely active UC who achieved clinical response (per Adapted Mayo score) following induction therapy from Study M14-234 Substudy 1, Substudy 2, or Study M14-675. Study M14-675 is an induction study in patients with moderately to severely active UC.

The secondary objective of Substudy 3 is to evaluate the efficacy of upadacitinib 30 mg QD and 15 mg QD compared to placebo in the ranked secondary endpoints at Week 52 of achieving endoscopic improvement, maintaining clinical remission, corticosteroid free remission, maintaining endoscopic improvement, endoscopic remission, maintaining clinical response, mucosal healing, no bowel urgency, no abdominal pain, histologic-endoscopic mucosal improvement, change in IBDQ total score and FACIT-F score.

Note: For subjects who entered Substudy 3 from Study M14-234 Substudy 1, these subjects were only required to complete 44 weeks of maintenance therapy in Substudy 3. At the time of this amendment, if a subject from Substudy 1 is in Substudy 3 and has not yet completed the Week 44 Visit, they will be re-consented to extend treatment to Week 52 after approval for the amendment has been obtained for each respective site. Subjects entering Substudy 3 from Study M14-234 Substudy 2 or Study M14-675 will be required to complete 52 weeks in Substudy 3 if they do not withdraw prior. At the time of this amendment, Substudy 3 has closed enrollment.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of upadacitinib as induction and maintenance therapy in subjects with moderately to severely active UC.

The study comprises 3 substudies: a Phase 2b dose-ranging induction substudy (Substudy 1), a Phase 3 dose-confirming induction substudy (Substudy 2), and a Phase 3 maintenance substudy (Substudy 3).

The study is designed to enroll approximately 844 subjects in Substudy 1 and Substudy 2 to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The study duration could be up to 77 weeks (excluding a possible washout period), including a Screening Period of up to 5 weeks, an 8-week double-blind Induction Period, an 8-week, open-label, Extended Treatment Period (for eligible subjects), a 52-week Maintenance Period, and a 30-day Follow-up Period. For subjects who meet criteria for loss of response during the Maintenance Period (Substudy 3), the Week 52/PD Visit should be conducted.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed. These measures will only be implemented under the protocol in countries that are affected by the COVID-19 pandemic.

Substudy 1

At the time of this amendment, Substudy 1 has closed and all subjects in Substudy 1 have completed the 8-week induction phase.

Subjects (n = 250) who met eligibility criteria were randomized in a 1:1:1:1:1 ratio to one of the following double-blinded induction treatment arms:

- Group 1: upadacitinib 7.5 mg QD (n = 50)
- Group 2: upadacitinib 15 mg QD (n = 50)
- Group 3: upadacitinib 30 mg QD (n = 50)

- Group 4: upadacitinib 45 mg QD (n = 50)
- Group 5: Placebo QD (n = 50)

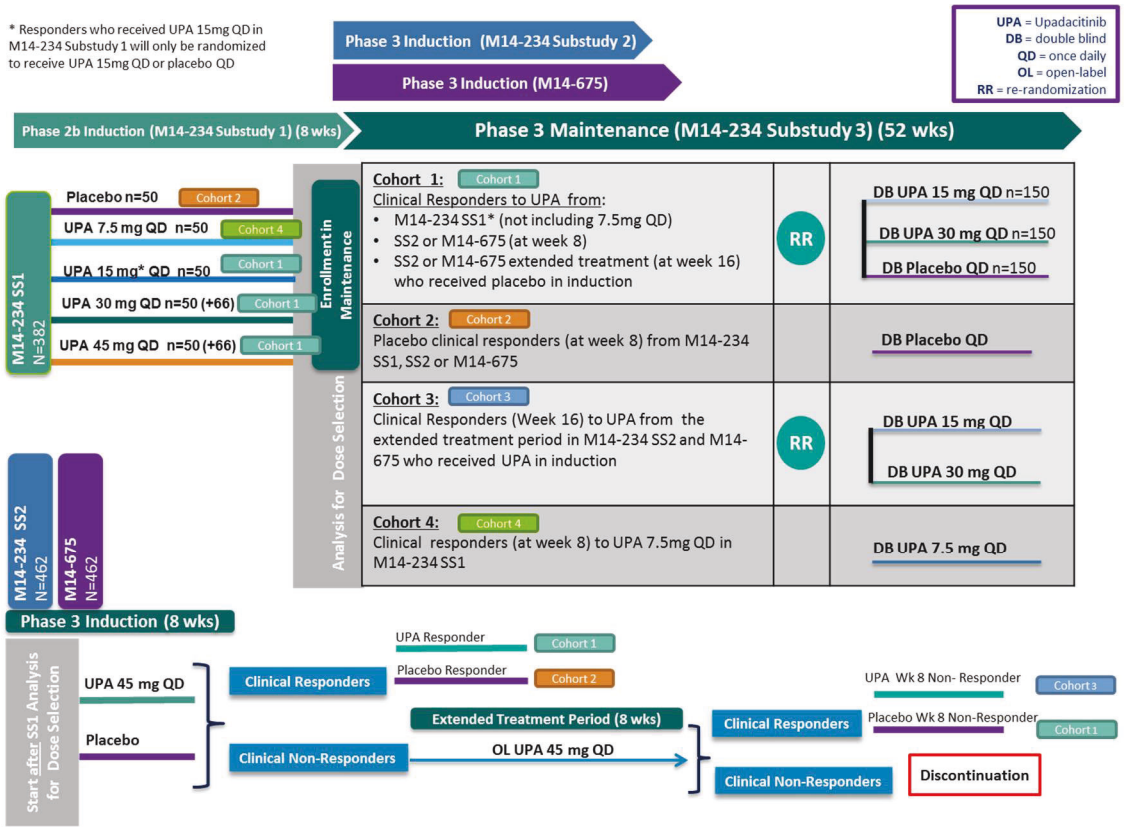
The population in Substudy 1 included subjects who demonstrated inadequate response to, loss of response to, or intolerance to biologic therapy (biologic inadequate responders [bio-IR]) and subjects who demonstrated inadequate response to, loss of response to, or intolerance to conventional therapy but had not failed biologic therapy (non-bio-IR). Approximately 75% of subjects enrolled were bio-IR and 25% of subjects were non-bio-IR in Substudy 1.

After the 250 randomized subjects completed the 8-week induction, an analysis of efficacy and safety (selected laboratory parameters) of upadacitinib versus placebo was performed. This analysis is referred to as dose-selection analysis thereafter. Based on this analysis, one induction dose (upadacitinib 45 mg) was identified for further evaluation in Substudy 2 and Study M14-675. The results of this analysis were reviewed and discussed with regulatory authorities, as applicable, prior to initiation of enrollment of subjects in Substudy 2 and/or Study M14-675.

During the analysis period, 132 additional subjects were randomized into Groups 3 and 4 of Substudy 1 (upadacitinib 30 mg QD and 45 mg QD dose groups; approximately 66 subjects per dose group). The objectives of enrolling these additional subjects are to avoid interrupting the study activities during the analysis period and to support a sufficient number of subjects with clinical response to be re-randomized into the maintenance portion in Substudy 3. The data collected from these subjects will be reported separately in the clinical study report.

Subjects in Substudy 1 who did not achieve clinical response after completion of the 8-week induction treatment had the option to enroll into a separate AbbVie Study M14-533, a Phase 3 multicenter long-term extension study. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and $\geq 30\%$ from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1.

Figure 1. Study M14-234 Overall Design Schematic



Abbreviations: SS1 = Substudy 1; SS2 = Substudy 2

Note: 132 additional subjects were randomized to upadacitinib 30 mg QD (~66 subjects) or upadacitinib 45 mg QD (~66 subjects) during the analysis for dose selection.

5.1.1 Substudy 2

At the time of this amendment, Substudy 2 has closed enrollment.

Subjects who consent and meet all of the inclusion and none of the exclusion criteria as defined in Section 5.2.1 and Section 5.2.2 will be enrolled into Substudy 2, which consists of two parts: (Part 1) a randomized, double-blind, placebo-controlled 8-week induction study; (Part 2) an 8-week Extended Treatment Period for clinical non-responders from Part 1 of Substudy 2.

In Substudy 2, the number of non-bio-IR subjects will be at least 25% and not exceed 50% and will allow enrollment of up to 30% of subjects who have failed 3 or more biologics among bio-IR subjects. In non-bio-IR subjects, subjects who have used a biologic up to 1 year and have discontinued for reasons other than inadequate response, loss of response, or intolerance (e.g., change of insurance/reimbursement, well-controlled disease, etc.) may be enrolled but must meet other criteria for inadequate response, loss of response, or intolerance to aminosalicylates, corticosteroids, or immunosuppressants as defined in the protocol. The study will allow for enrollment of up to 20% enrolled non-bio-IR subjects who could also have previous use of a biologic therapy but discontinued based on reasons other than inadequate response, loss of response, or intolerance. Substudy 2 will also evaluate the efficacy of an additional 8-week upadacitinib 45 mg QD treatment in subjects who did not achieve clinical response in the initial 8-week induction phase.

In Part 1, approximately 462 subjects will be enrolled. Eligible subjects will be randomized in a 2:1 ratio to one of the two treatment groups (double-blind upadacitinib 45 mg QD or matching placebo) for 8 weeks. The randomization will be stratified by bio-IR status (bio-IR vs non-bio-IR), corticosteroid use (yes or no), and Adapted Mayo score (≤ 7 or > 7) at Baseline. Within bio-IR, the randomization will be further stratified by number of prior biologic treatments (≤ 1 or > 1). Within non-bio-IR, the randomization will be further stratified by previous biologic use (yes or no).

The following are the treatment groups for Part 1 of Substudy 2:

- **Group 1:** Upadacitinib 45 mg QD (blinded, n = 308)
- **Group 2:** Placebo QD (blinded, n = 154)

Part 2 is an open label, 8-week Extended Treatment Period for subjects who did not achieve clinical response at Week 8 in Part 1. The objectives of Part 2 are to offer upadacitinib induction treatment to placebo clinical non-responders (defined by Adapted Mayo Score) from Part 1, and to evaluate delayed clinical response to upadacitinib in subjects who do not initially respond to upadacitinib during Part 1.

During COVID-19 pandemic, investigators should make the best effort to perform the endoscopies required per protocol. For subjects with missing endoscopy at Week 8/16 when endoscopies cannot be performed due to the COVID-19 pandemic, the site should assess the status of clinical response defined by the Partial Adapted Mayo Score. If the subject is a clinical responder at Week 8/16, the subject may enter Study M14-533 Cohort 1. If the subject is a clinial non-responder at Week 8, the subject may enter Part 2. If the subject is a clinical non-responder at Week 16 the subject will discontinue from the study. A notification should be sent to the TAMD as to the responder status and which part of the program the subject will be going to prior to the transfer taking place.

The blind from Substudy 2 Part 1 will be maintained as these subjects will be assessed simply as non-responders and moved to Substudy 2 Part 2 for further treatment in the study. All eligible subjects entering Part 2 will receive open-label treatment with upadacitinib 45 mg QD for 8 additional weeks (until Week 16).

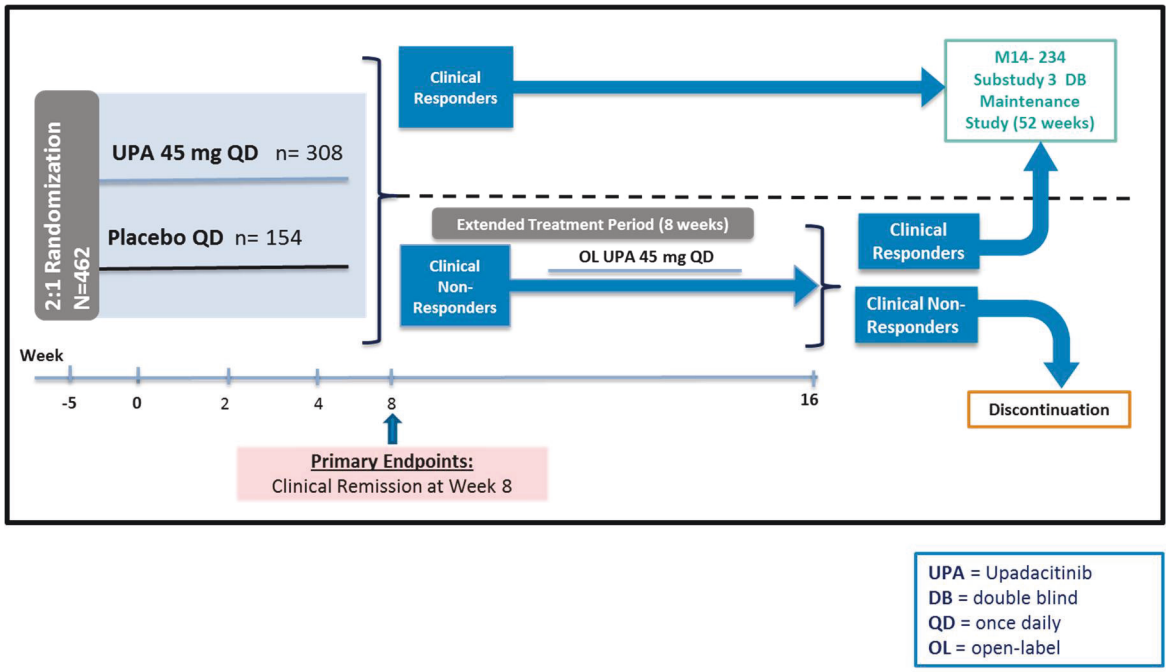
Subjects who achieve clinical response defined by Adapted Mayo Score at Week 8 or Week 16 will be eligible to enroll into Substudy 3. Subjects with missing Week 8 or/and Week 16 endoscopy during the period of COVID-19 pandemic will not be eligible to enter Substudy 3. Subjects who do not achieve clinical response at Week 16 will be discontinued from the study and will not be eligible to enroll in Study M14-533 (long-term extension).

The data collected from subjects in Part 2 will not be part of the primary efficacy analysis for the induction study; descriptive statistics will be used, and the results will be reported separately in the clinical study report.

Subjects are not eligible to enter into Part 2 until the Week 8 endoscopy has been completed, except for subjects missing endoscopy due to COVID-19 pandemic. The central reader will also review the endoscopy video, but movement of the subject to Substudy 2 Part 2 will be based on the local reader scoring. Visits in Part 2 will occur at Week 10, 12, 14, and 16, and an endoscopy will be performed at Week 16. Flexible sigmoidoscopy is recommended, however the use of colonoscopy or flexible sigmoidoscopy is in the investigator's discretion based on local practice.

Figure 2 shows the schematic for Substudy 2.

Figure 2. Study M14-234 Substudy 2 Schematic



5.1.2 Substudy 3

Approximately 750 subjects who achieved clinical response per Adapted Mayo Score after completion of induction treatment or Extended Treatment Period in Study M14-234 Substudy 1, Substudy 2, or Study M14-675 will be eligible to enter Substudy 3 and treated with a blinded treatment assignment for up to 52 weeks. Subjects with missing Week 8 or/and Week 16 endoscopy during the period of COVID-19 pandemic will not be eligible to enter Substudy 3. Subjects who completed Study M14-675 will consent for Study M14-234 prior to entering Substudy 3. The only eligibility checks required for a subject to enter Study M14-234 Substudy 3 from Study M14-675 is to consent to the Study M14-234 Substudy 3 and to have achieved clinical response at Week 8 or 16 of Study M14-675 and do not meet any study discontinuation criteria, meeting the Protocol listed inclusion and exclusion criteria for Study M14-234 is not required for these subjects at this point of transition. The Baseline Visit of Substudy 3 is completed on the same day as the final visit in the Induction Phase (either at Week 8 or Week 16) for subjects who are eligible.

Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. The treatment assignment in Substudy 3 will depend on the treatment received in Substudies 1 and 2, or Study M14-675, as detailed below.

Substudy 3 will include 4 cohorts:

Cohort 1:

Approximately 525 subjects who achieved clinical response in Study M14-234 Substudies 1 and 2, or Study M14-675, and received 1 of the following treatments will be re-randomized in a 1:1:1 ratio to one of the treatment groups in Cohort 1:

- Upadacitinib 30 mg QD or 45 mg QD in Study M14-234 Substudy 1
- Upadacitinib 45 mg QD in Study M14-234 Substudy 2 Part 1
- Upadacitinib 45 mg QD in Study M14-675 Part 1

- Placebo QD in Study M14-234 Substudy 2 Part 1 followed by upadacitinib 45 mg QD in Study M14-234 Substudy 2 Part 2
- Placebo QD in Study M14-675 Part 1 followed by upadacitinib 45 mg QD in Part 2

Treatment groups in Cohort 1:

- Group 1: upadacitinib 15 mg QD
- Group 2: upadacitinib 30 mg QD
- Group 3: placebo QD

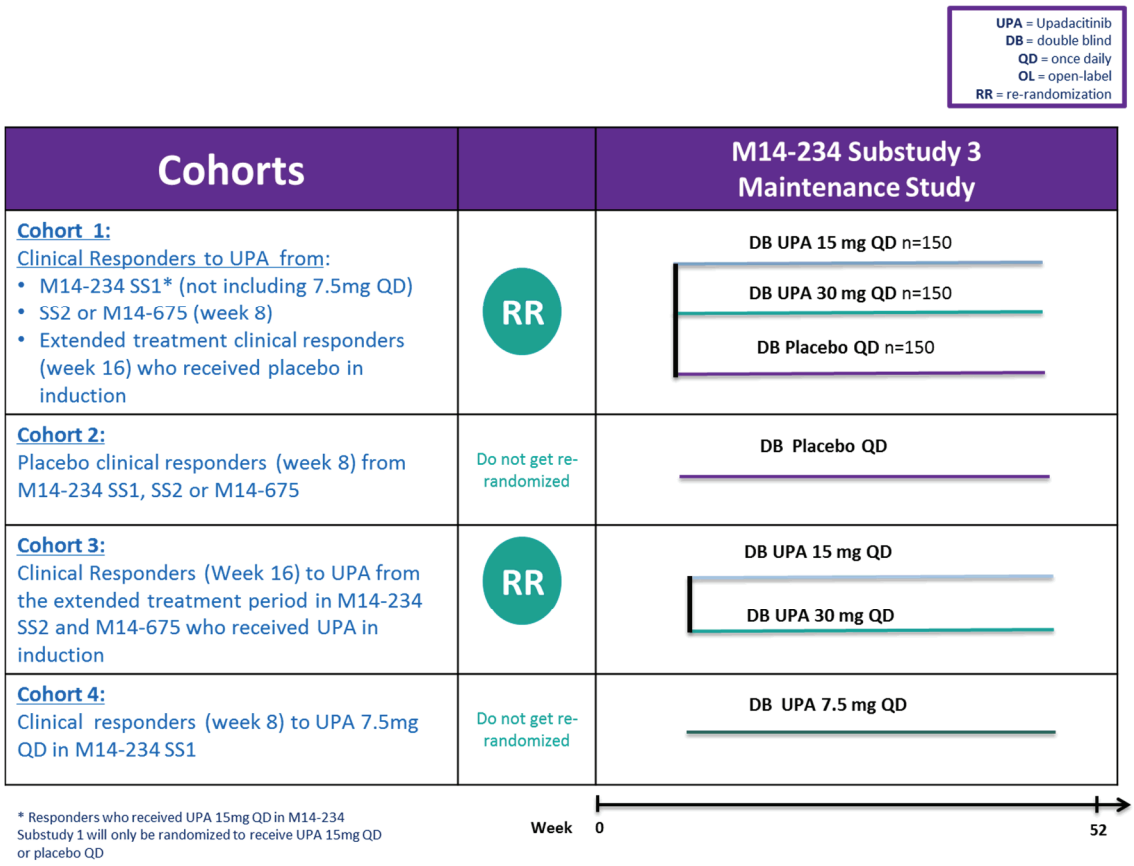
Subjects who achieved clinical response and received upadacitinib 15 mg QD in Study M14-234 Substudy 1 will be re-randomized 1:1 to only receive upadacitinib 15 mg QD or placebo QD (treatment Group 1 or 3).

Cohort 2: approximately 60 subjects who received double-blind placebo QD treatment for 8 weeks during Study M14-234 Substudy 1, Substudy 2 Part 1 or Study M14-675 Part 1 and achieved clinical response will continue to receive blinded placebo QD in Substudy 3.

Cohort 3: approximately 150 subjects who received upadacitinib 45 mg QD in induction phase and did not achieve clinical response - and received upadacitinib 45 mg in Extended Treatment in Study M14-234 (Substudy 2, Part 2) or Study M14-675 (Part 2) and achieved clinical response at Week 16 will be re-randomized 1:1 and receive blinded upadacitinib 30 mg QD or upadacitinib 15 mg QD in Study M14-234 (Substudy 3).

Cohort 4: approximately 15 subjects who received double-blinded treatment of upadacitinib 7.5 mg for 8 weeks during Study M14-234 (Substudy 1) and achieved clinical response will continue to receive blinded treatment of upadacitinib 7.5 mg QD in Substudy 3. The schematic of Substudy 3 is shown in Figure 3.

Figure 3. Study M14-234 Substudy 3 Schematic



The rationale for re-randomizing only induction responders who received upadacitinib 15, 30 or 45 mg QD from Substudy 1 is to ensure that no subject receives a dose during maintenance that is higher than what was received in the induction period.

During Substudy 3, subjects who meet the criteria for initial loss of response after at least 2 weeks of treatment and have a second confirmed loss of response on a consecutive visit at least 14 days later will have the option to enroll into Study M14-533 and receive open-label upadacitinib. Timely data entry regarding loss of response is required and should not be done retrospectively to ensure accurate calculations.

Loss of response is defined as follows:

- A subject who presents with an SFS and RBS score each at least 1 point greater than the end-of-induction value (Week 8 of Substudy 1, Substudy 2 Part 1, Study M14-675 Part 1 or Week 16 of Substudy 2 Part 2 or Study M14-675 Part 2) on two consecutive visits at least 14 days apart, associated with the presence of signs or symptoms of progression of UC disease as assessed by the investigator.

For subjects with SFS or RBS ≥ 2.1 at the end-of-induction, loss of response is defined as:

- An increase in either the SFS or RBS of at least 1 point greater than the end-of-induction value on two consecutive visits at least 14 days apart and associated with the presence of signs or symptoms of progression of UC disease as assessed by the investigator.

Confirmation of loss of response may be performed at either the next scheduled visit or at an Unscheduled Visit. For subjects who meet criteria for loss of response during the maintenance period (Substudy 3), the Week 52/PD Visit should be conducted.

The duration of the study could be up to 77 weeks, including Screening Period (5 weeks), an 8-week Double-Blind Induction Period, an 8-week Open-Label Extended Treatment Period (for eligible subjects), a 52-week Maintenance Period, and a 30-day Follow-Up Period.

Note: Subjects who entered Substudy 3 from Study M14-234 Substudy 1 were only required to complete 44 weeks of maintenance therapy in Substudy 3. At the time of this amendment, if a subject from Substudy 1 is in Substudy 3 and has not yet completed the Week 44 Visit, they will be re-consented to extend treatment to Week 52 after approval for the amendment has been obtained for each respective site. Subjects entering Substudy 3 from Study M14-234 Substudy 2 or from Study M14-675 will be required to complete 52 weeks in Substudy 3 if they do not withdraw or have loss of response prior.

Screening

Subjects should receive a full explanation of the study design and study procedures and provide a written informed consent prior to performing any screening procedure. Once written informed consent is obtained, subjects will undergo screening procedures as outlined in Appendix C with a maximum of 35 days allowed for the screening period. The Baseline Visit can be scheduled and a subject randomized at any point during this 35-day period once all eligibility criteria have been met.

An electronic diary (e-diary) will be dispensed and training will be provided to the subject at the Screening Visit in Study M14-234 or Study M14-675 (see Section 10.3 details).

With the exception of the QuantiFERON TB-Gold Plus and PPD tests (requirements outlined in Section 5.3.1 [Clinical Laboratory Tests]), exclusionary 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.

Subjects, who have been taking exclusionary medications prior to screening or Baseline must complete medication washout. The duration is based on the excluded medication as described in the protocol. 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 or later from the last dose; (2) adalimumab, certolizumab, golimumab, or vedolizumab: may be tested approximately 6 weeks or later from the last dose; (3) ustekinumab: may be tested approximately 8 weeks or later 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.

Protocol-related adverse events should be reviewed and subjects must complete the washout prior to the Baseline Visit.

If some subjects screen and are unable to enter Substudy 2 due to enrollment limits, these subjects may be moved to Study M14-675 for induction treatment if enrollment limits on that study have not been fulfilled.

8-Week Induction Period – Substudy 1 and Substudy 2 Part 1

This period will begin at the Baseline Visit (Week 0) and will end at the Week 8 Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 for the respective substudy will be enrolled into the study and randomized to the double-blind induction period. During this period of the study, subjects will visit the study site at Weeks 2, 4, 6, and 8. A ± 3-day window is permitted around scheduled study visits. The last dose of study drug during this period is recommended to be taken the day prior to the Week 8 Visit when possible.

8-Week Extended Treatment Period – Substudy 2 Part 2

The period will begin after the Week 8 endoscopy in Substudy 2, Part 1 and will end at the Week 16 Visit. Substudy 1 subjects will not be eligible for this portion of the study.

At Week 8, subjects in Substudy 2, Part 1 who did not achieve clinical response (defined by Adapted Mayo Score) will be enrolled into Part 2 and receive open-label upadacitinib 45 mg QD for an additional 8 weeks. Clinical response is defined as decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1.

During COVID-19 pandemic, investigators should make the best effort to perform the endoscopies required per protocol. For subjects with missing endoscopy at Week 8/16 when endoscopies cannot be performed due to the COVID-19 pandemic, the site should assess the status of clinical response defined by the Partial Adapted Mayo Score. If the subject is a clinical responder at Week 8/16, the subject may enter Study M14-533 Cohort 1. If the subject is a clinical non-responder at Week 8, the subject may enter Part 2. If the subject is a clinical non-responder at Week 16 the subject will discontinue

from the study. A notification should be sent to the TAMD as to the responder status and which part of the program the subject will be going to prior to the transfer taking place.

During this period of the study, subjects will visit the study site at Weeks 10, 12, 14, and 16. A ± 3-day window is permitted around scheduled study visits. The last dose of study drug during this period is recommended to be taken the day prior to the Week 16 Visit when possible.

52-Week Maintenance Period – Substudy 3

Subjects in Substudies 1 and 2 or Study M14-675 who achieved clinical response per Adapted Mayo Score after completion of the 8-Week Induction Period or the Week 16 Visit of the Extended Treatment Period, if applicable, will be enrolled in Substudy 3. Subjects who completed Study M14-675 will consent for Study M14-234 prior to entering Substudy 3. This period will begin at the Baseline (Week 0) Visit (Week 8 or Week 16 of Substudy 1, Substudy 2, or Study M14-675) and will end at the Week 52 Visit. Treatment in Substudy 3 will depend on the treatment received in Substudies 1 and 2 or Study M14-675, as described in Section 5.1. During this period of the study, subjects will visit the study site at Weeks 4, 8, 12, 20, 28, 36, 44, and 52. A ± 3-day window is permitted around scheduled study visits up to and including Week 12. Following completion of the Week 12 visit, a ± 7-day window is permitted around scheduled study visits. The final dose of study drug is taken the day prior to the Week 52 Visit.

Re-Screen

Subjects that initially screen fail for the study will be permitted to re-screen following re-consent. For any subjects who screened and who were unable to enter the program during Substudy 1 due to enrollment limits, these subjects may also be rescreened into Substudy 2 **or** Study M14-675.

The subject must meet all the inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study and there is no maximum number of re-screens

allowed for a given subject. If the subject had a complete initial screening evaluation including the assessment of a purified protein derivative (PPD) test (or equivalent), or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold Plus test or T-SPOT TB test), chest x-ray, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, Beta-D-glucan (Japan only) and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 calendar days have passed since the date of the testing.

If a subject is being rescreened within 14 days (from the date of the previous screening testing), it is not required to repeat Screening testing for chemistry/hematology, urinalysis, serum pregnancy, and *Clostridium difficile* (*C. difficile*).

An endoscopy with biopsy will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and re-consent is no more than 30 calendar days after the initial screening endoscopy.

All other screening procedures will be repeated. As appropriate, sites are encouraged to contact the AbbVie TA MD to confirm if subjects should or should not be re-screened.

Re-screened subjects will retain the same subject number assigned at the initial screening.

5.2 Selection of Study Population

It is anticipated that approximately 844 subjects (382 in Substudy 1 and approximately 462 in Substudy 2) with moderately to severely active UC who meet all of the inclusion criteria and none of the exclusion criteria will be randomized at approximately 400 study centers worldwide. Approximately 750 subjects from Substudies 1, 2 or Study M14-675 who achieve response per Adapted Mayo score following induction with upadacitinib will be re-randomized into Substudy 3 (maintenance).

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

5.2.1 Inclusion Criteria

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

1. Male or female ≥ 16 and ≤ 75 years of age at Baseline.
   - Adolescent subjects at the age of 16 and 17 years old will be enrolled if approved by the country or regulatory/health authority. If these approvals have not been granted, only subjects ≥ 18 years old will be enrolled.
   - Adolescent subjects at the age of 16 and 17 years old must weigh ≥ 40 kg and meet the definition of Tanner Stage 5 (refer to Appendix J) at the screening Visit.
2. Diagnosis of UC for 90 days or greater prior to Baseline, confirmed by colonoscopy during the Screening Period, with exclusion of current infection, colonic dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.
3. Active UC with an Adapted Mayo Score of 5 to 9 points and endoscopy subscore of 2 to 3 (confirmed by central reader).
4. Demonstrated an inadequate response to, loss of response to, or intolerance to at least one of the following treatments including, oral aminosalicylates, corticosteroids, immunosuppressants and/or biologic therapies, in the opinion of the investigator as defined below:

   Note: An inadequate response, loss of response, or intolerance to Oral Aminosalicylates will NOT count towards eligibility for the following countries: Austria, Czechia, Finland, France, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Spain, Sweden and United Kingdom.

   - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide)
     - Signs and symptoms of persistently active disease, in the opinion of the investigator, during a current or prior course of at least 4 weeks of

treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide.

- Corticosteroids
  - Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥ 40 mg/day orally for at least 3 weeks or intravenously for 1 week, OR
  - Unable to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease, OR
  - Signs and symptoms of persistently active disease during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone, OR
  - Unable to taper oral budesonide to at or below 6 mg/day without recurrent active disease, OR
  - History of intolerance to corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection).
- Immunosuppressants
  - Signs and symptoms of persistently active disease despite a history of at least one 90 day regimen of oral azathioprine (≥ 1.5 mg/kg/day; for subjects in Japan, China, and Taiwan only: ≥ 1.0 mg/kg/day), 6-MP (≥ 1 mg/kg/day; [for subjects in Japan, China, and Taiwan only: ≥ 0.6 mg/kg/day, rounded to the nearest available tablet of half tablet formulation] or a documented 6-TGN level of 230 – 450 pmol/8 × 10^8 RBC or higher on the current dosing regimen), injectable MTX (≥ 15 mg/week subcutaneous [SC] or intramuscular), or tacrolimus (for subjects in Japan and Taiwan only: documented trough level of 5 – 10 ng/mL), ***OR***
  - History of intolerance to at least one immunosuppressant (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, infection)

Note: Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study unless these subjects were previously treated with aminosalicylates, corticosteroids or

immunosuppressants (azathioprine or 6-MP) and have inadequate response to, loss of response to or intolerance to the therapy as defined above.

- Biologic Agents for UC
  - Signs and symptoms of persistently active disease despite a history of any of the following:
    - at least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at 0, 2, and 6 weeks),
    - at least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous (SC) dose followed by one 80 mg SC dose [or one 80 mg SC dose, in countries where this dosing regimen is allowed] followed by one 40 mg SC dose at least 2 weeks apart),
    - at least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart),
    - at least one 6-week induction regimen of vedolizumab (300 mg IV at 0, 2 and 6 weeks),
    - at least one induction regimen of ustekinumab, a single IV dose using weight-based dosing (260 mg for subjects with body ≤ 55 kg; 390 mg for subjects with body weight > 55 kg and ≤ 85 kg; 520 mg for subjects with body weight > 85 kg OR
  - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), OR
  - History of intolerance to at least one biologic agent (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

  Note: Non-bio-IR subjects who have received a prior biologic for up to 1 year may be enrolled, however, subjects must have discontinued the biologic for reasons other than inadequate response or intolerance (e.g., change of insurance, well controlled disease), and must meet the criteria for inadequate response, loss of response or intolerance to aminosalicylates, corticorsteroids and/or immunosuppressants as defined above.

5. Female subjects of childbearing potential (refer to Section 5.2.4) must have a negative serum pregnancy test at the Screening Visit and 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 borderline result and a serum pregnancy test ≥ 3 days later to document continued lack of positive result. For subjects in Ireland and Argentina, a repeat serum pregnancy test ≥ 3 days later that is still borderline will result in screen failure.

6. If female, subject must meet the criteria as stated in Section 5.2.4 Contraception Recommendations.

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

8. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.

Rationale for the Inclusion Criteria

Criteria	Rationale
1 – 4, 7	In order to select the appropriate subject population with a disease status representative of the target population for evaluation
5 – 6	The effect of upadacitinib on pregnancy and reproduction is unknown
8	In accordance with good clinical practice (GCP) and in order to select subjects who will comply with study procedures for adequate evaluation

5.2.2 Exclusion Criteria

1. Subject with current diagnosis of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy.
4. History of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy or is planning bowel surgery.
5. Received treatment with rectal aminosalicylates or corticosteroids, other enemas/suppositories (other than required for endoscopy), within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
6. Received cyclosporine, tacrolimus, mycophenolate mofetil or thalidomide within 30 days prior to Baseline.
7. Subjects who received azathioprine or 6-mercaptopurine within 10 days of Baseline.
8. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
9. Subject on MTX or oral aminosalicylates who:
   - has not been on the current course of MTX for at least 42 days prior to Baseline, and has not been on stable doses for at least 28 days prior to Baseline;
   - has not been on stable doses of oral aminosalicylates for at least 14 days prior to Baseline;
   - has discontinued use of aminosalicylates within 14 days of Baseline.
10. Subject on treatment with corticosteroids who meet the following:
    - Oral corticosteroid dose > 30 mg/day (prednisone or equivalent) 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;

- Oral budesonide dose > 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
- Oral beclomethasone dose > 5 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
- 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.

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

12. Subject who received fecal microbial transplantation within 30 days prior to Baseline.

13. Subject on UC-related antibiotics who has not been on stable doses for at least 14 days prior to Baseline or has discontinued these medications within 14 days of Baseline.

14. Subjects who received any of the following biologic therapy:

    - infliximab, certolizumab, adalimumab, golimumab, vedolizumab, natalizumab, within 8 weeks prior to Baseline. OR
    - ustekinumab within 12 weeks prior to Baseline

      Note: If there is proper documentation of undetectable drug level measured by a commercially available assay for any of the approved biologics above, there is no minimum washout prior to Baseline.

15. Subject with previous exposure to JAK inhibitor (e.g., tofacitinib, baricitinib, filgotinib, upadacitinib).

16. Subject who received non-steroidal anti-inflammatory drugs (NSAIDs) (except topical NSAIDs and the use of low dose aspirin for cardiovascular [CV] protection) within 7 days prior to Baseline.

17. Subject received traditional Chinese medicine within 30 days prior to baseline.

18. Subject received live vaccine(s) within 30 days (8 weeks for Japan) prior to Baseline, or who is expected to need live vaccination during study participation including at least 30 days (or longer if required locally) (8 weeks for Japan) after the last dose of study drug.

19. Systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers during the Screening Period and through the end of the study, as specified in Section 5.2.3.3.

20. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during study treatment.

21. Subject who received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer, or is currently enrolled in an interventional study.

22. Subject with positive C. difficile toxin stool assay during Screening.

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

24. Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study

25. Subject has current or past history of recurrent or disseminated (even a single episode) herpes zoster

26. Subject has current or past history of disseminated (even a single episode) herpes simplex

27. Subject has HBV, HCV, or human immunodeficiency virus (HIV) infection 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 subjects who are hepatitis B core antibody (HBc Ab)

positive (+) subjects (and for Hepatitis B surface antibody positive (+) subjects where mandated by local requirements);

- HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab);
- HIV: confirmed positive anti-HIV antibody (HIV Ab).

28. Prior or current gastrointestinal (GI) dysplasia, other than completely removed low-grade dysplastic lesion in any biopsy performed during or before the Screening endoscopy.

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

30. History of spontaneous gastrointestinal (GI) perforation (other than appendicitis or mechanical injury), diverticulitis or significantly increased risk of GI perforation per investigator's judgment.

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

- Serum Aspartate Transaminase (AST) or Alanine Transaminase (ALT) > 2 × upper limit of normal (ULN);
- Estimated glomerular filtration rate (eGFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 mL/min/1.73 m^2;
- Total White Blood Cell (WBC) count < 2,500/µL;
- Absolute neutrophil count (ANC) < 1,200/µL;
- Platelet count < 100,000/µL;
- Absolute lymphocytes count < 750/µL;
- Hemoglobin < 9 g/dL.

32. Female subject who is pregnant, breastfeeding or considering becoming pregnant during the study and within 30 days after the last dose of study drug, or has positive pregnancy test at Screening (serum) or Baseline (urine).

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

34. History of clinically significant (per investigator's judgment) drug or alcohol abuse in the last 6 months.

35. Subject who previously received stem cell transplantation

36. Subject has been a previous recipient of an organ transplant which requires continued immunosuppression.

37. For Japan subjects only: positive result of beta-D-glucan or two consecutive indeterminate results of beta-D-glucan (screening for Pneumocystis jiroveci infection)

38. Received cytapheresis treatment (GCAP, LCAP etc.) within 60 days prior to Screening.

39. For Japan subjects only: received ATM treatment (antibiotic combination therapy with amoxicillin, tetracycline and metronidazole) during the Screening Period.

40. Any of the following cardiovascular or thrombotic conditions:
    - Recent (within past 6 months) cerebrovascular accident, myocardial infarction or coronary stenting
    - Recent (within past 6 months) moderate to severe congestive heart failure (New York Heart Association class III or IV);
    - Prior history of thrombotic events, including deep vein thrombosis and pulmonary embolism
    - Known inherited conditions that predispose to hypercoagulability

41. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome or gastric bypass surgery; subjects with a history of gastric banding/segmentation are not excluded.

42. History of clinically significant medical condition or any other reason which, in the opinion of the investigator, would interfere with the subject's participation in this

study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the protocol.

Rationale for the Exclusion Criteria

Criteria	Rationale
1 – 19	To select the appropriate subject population
20 – 31, 33 – 42	To ensure safety of the subjects throughout the study
32	The impact of upadacitinib on pregnancies is unknown

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

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

If subjects have/had ever been treated with including, but not limited to UC-related antibiotics, corticosteroid, immunosuppressant, aminosalicylates 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 history of previous use (including the duration of therapy, the highest known dose taken, reason for use and reason[s] for termination of treatment) of UC-related corticosteroids, immunosuppressant, aminosalicylates, UC-related antibiotics, or biologic agents will be recorded in the appropriate eCRF.

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

5.2.3.2 Concomitant Therapy

Concomitant UC-Related Medications (Oral Corticosteroids, Antibiotics, Aminosalicylates, and/or Methotrexate):

Substudies 1 and 2

All UC-related concomitant medications should be kept on the stable dose in Substudies 1 and 2. Dose may be decrease or terminated in the event of moderate-to-severe treatmentrelated toxicity (e.g., leukopenia or elevated liver enzymes) in the opinion of the investigator.

Substudy 3

At Baseline of Substudy 3 (Week 8 or Week 16 of Study M14-234 Substudy 1, Substudy 2, and Study M14-675), subjects who are taking corticosteroid therapy will have their corticosteroid therapy tapered according to a proposed tapering schedule specified in Section 5.3.1.1 in the Protocol. Subjects taking corticosteroids who have worsening of disease per the investigator's judgment after the steroid taper has been initiated may have their corticosteroid dose increased per the investigator's discretion during the study. Use of inhaled or topical dermatologic corticosteroids is not restricted.

All subjects receiving UC-related antibiotics may discontinue treatment starting at Week 0 of Substudy 3 at the discretion of the investigator.

All subjects receiving stable dose of UC-related antibiotics (those subjects who did not discontinue), aminosalicylates, or MTX at Week 0 will maintain their concomitant treatments and respective doses through the end of the study. Dose may be decreased or terminated in the event of moderate to severe treatment related toxicity (e.g., leukopenia or elevated liver enzymes) in the opinion of the investigator.

Changes in all concomitant medications will be assessed at each study visit from Baseline (Week 0) through Week 8/PD Visits in Substudies 1 and 2 or Study M14-675; through Week 16/PD Visits in the extended treatment periods of Substudy 2 or Study M14-675; and through Week 52/PD Visits in Substudy 3. Any changes will be documented in the source documents and captured on the appropriate eCRF page.

Vaccines

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap).

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (per local label) at least 30 days (8 weeks for subjects in Japan) before first dose of study drug. Live vaccinations are prohibited during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.

If the live herpes zoster vaccine is to be administered and there is no known history of primary varicella (chicken pox), preexisting 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 live herpes zoster vaccine should not be administered.

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

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

Biologic Therapies

Subjects must have discontinued any biologic therapy prior to the first dose of study drug as specified in the washout procedures (Exclusion Criterion 14, Section 5.2.2). For all other biologic therapies the required washout period is at least five times the mean terminal elimination half-life of the medication prior to the first dose of study drug. No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented.

- All biologic therapy including but not limited to the following:
  - Etanercept;
  - Abatacept;
  - Anakinra;
  - Rituximab;
  - Natalizumab;
  - Tocilizumab;
  - Efalizumab;
  - Ustekinumab;
  - Belimumab;
  - Golimumab;
  - Vedolizumab;
  - Infliximab;
  - Adalimumab;
  - Certolizumab pegol
  - Secukinumab
- Other JAK inhibitors (e.g., tofacitinib [Xeljanz®], ruxolitinib [Jakafi®], baricitinib [Olumiant®], peficitinib, [Smyraf®], abrocitinib [PF-04965842], and filgotinib)

- **Vaccines**

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (per local label) at least 30 days (8 weeks for subjects in Japan) before first dose of study drug (see Section 5.2.3 Prior and Concomitant Therapy). Live vaccinations are prohibited during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.

- 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).

Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid or biosynthetic include, but are not limited to, injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted) and pertussis (Tdap) vaccines.

Other Medications

- Intravenous corticosteroid use is prohibited within 14 days prior to Screening or during the Screening Period and during the study, unless administered as rescue

therapy due to worsening of UC in Substudy 3. (Initiating rectal or systemic corticosteroids use is prohibited during the induction and maintenance treatment period. Rectal or systemic corticosteroids may be used as rescue therapy at the investigator's discretion for subjects as rescue therapy in Substudy 3; Patients who initiate rectal or systemic corticosteroid for any reason during the study must be discussed with the TA MD)

- Rectal aminosalicylates or corticosteroid enemas/suppositories are prohibited within 14 days prior to Screening endoscopy, during the remainder of the Screening Period, and during the study, unless administered as rescue therapy due to worsening of UC in Substudy 3
- Cyclosporine, tacrolimus, mycophenolate mofetil or thalidomide use is prohibited within 30 days prior to Baseline and during the study.
- Azathioprine or 6-mercaptopurine (6-MP) use is prohibited within 10 days prior to Baseline and during the study.
- NSAID (except topical NSAIDs and the use of low dose aspirin for cardiovascular protection) within 7 days prior to Baseline and during the study.

  Total parenteral nutrition is prohibited during the study.
- Cytapheresis treatment is prohibited within 60 days prior to Screening and during the study.
- Concomitant cannabis use, either recreational or for medical reasons, is prohibited at least 14 days prior to Baseline and during the study.
- Traditional Chinese medicines are prohibited within 30 days prior to Baseline and during the study.

Investigational Drugs

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

Strong CYP3A Inhibitors or Inducers

- Systemic use of strong CYP3A inhibitors or strong CYP3A inducers is prohibited from the Screening Visit through the end of the study. Examples of the most common strong CYP3A inhibitors and inducers are shown below:

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

In Japan, the following therapies are also prohibited:

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

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

5.2.3.4 Rescue Therapy

At or after Week 4 in Substudy 3, subjects who demonstrate loss of response and require medical treatment but have not met the criteria to enter Study M14-533 Cohort 1, may

receive rescue therapy. Rescue therapy may be provided in the form of initiation or increased dosage, at the investigator's discretion, of allowed UC-related medications to treat new or worsening UC symptoms. The allowed UC-related medications are locally acting, oral, or intravenous corticosteroids, aminosalicylates, MTX or UC-related antibiotics.

Anti-diarrheals for control of diarrhea are not considered rescue treatment. Azathioprine (AZA), 6-mercaptopurine (6-MP), cyclosporine, tacrolimus, and thalidomide are prohibited medications during the study and cannot be used as rescue treatment.

Changes in UC-related concomitant medications should be documented in the appropriate eCRF. Rescue therapy should not be withheld even if subject does not meet the criteria for loss of response or before 4 weeks after entering Substudy 3 if in the opinion of the investigator, failure to prescribe them would compromise the subject's safety. Subjects may also be discontinued at any time based on the investigator's medical assessment.

For subjects receiving corticosteroids as a rescue treatment, the investigator is encouraged to initiate tapering based on the subject clinical response status.

5.2.4 Contraception Recommendations

Contraception Recommendation for Females

Subjects must follow the following contraceptive guidelines as specified.

Females of Non-Childbearing Potential:

Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

- Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.

- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

Females of Childbearing Potential:

Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug. Females must commit to one of the following methods of highly effective birth control:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Baseline.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Baseline.
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure) (For Japan: only bilateral tubal ligation).
- Vasectomized partner(s) provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- 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 <u>not</u> 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).

For subjects in the US, Colombia, and where appropriate per local requirements, females of childbearing potential must commit to using two methods of contraception (either two highly effective methods or one highly effective method combined with one effective method). Effective methods of birth control are the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to study Baseline.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier method).

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

Refer to Section 5.3.1.1 for information on Pregnancy Testing.

5.3 Efficacy and Safety Assessments/Variables

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

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 the Study Activities in Appendix C through Appendix F are discussed in detail in this section, with the exception of exploratory research and validation studies (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, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, Informed Consent Form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. A separate informed consent will be required for each subject in order to participate in the optional exploratory research and validation studies. For US subjects only: at the end of the induction period (Week 8 or Week 16 of Substudy 1, Substudy 2, or Section M14-675), the subject will sign and date a study specific IEC/IRB approved Informed Consent Form before Substudy 3 procedures are performed; a separate informed consent will be required for each subject in order to participate in the Substudy 3 optional exploratory research and validation studies. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Subjects, who have been taking exclusionary medications prior to screening must complete medication washout. The duration is based on the excluded medication as described in the protocol. Protocol-related adverse events should be reviewed and subjects must complete the washout prior to the baseline visit.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, 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 medical and surgical history, including UC-onset date, history of UC medication use, and history of alcohol and tobacco use will be obtained from each subject at the Screening Visit. 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, and updated as necessary.

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

A detailed biologic therapy history (e.g., anti-TNF, anti-adhesion therapies) will be recorded, this includes names of biologic therapy used, duration of therapy, doses, reason(s) for use and reason(s) for termination of treatment with these products must be documented in the subjects' source documents and in the appropriate eCRF.

A detailed medical history with respect to inadequate response, loss of response and/or intolerance to aminosalicylates, immuno-modulators, corticosteroids and/or biologic therapies must be documented in the subjects' source documents. A detailed medical history with respect to TB exposure will be documented. This information will include BCG vaccination, cohabitation with individuals who have had TB, and residence or work in TB endemic locations.

Physical Examination

A full physical examination will be required to be performed at Screening, Baseline and Week 8 and Premature Discontinuation Visit (Substudies 1 and 2 or Study M14-675), Week 16 and Premature Discontinuation Visit (Substudy 2 or Study M14-675), Week 52 and Premature Discontinuation Visit (Substudy 3) and must include an assessment of extra-intestinal manifestations (EIMs).

For subjects aged 16 or 17 a Tanner Stage assessment will be completed at the screening visit to confirm eligibility. This may be completed by the investigator or by self-assessment (completed by the subject/legally authorized representative) per local requirements. If completed by self-assessment, site is responsible for training the subject/legally authorized representative appropriately.

The physical examination at the Baseline Visit will serve as the Baseline physical examination for the entire study. Abnormalities noted after the Baseline Visit and first dose of study drug will be evaluated and documented by the investigator as to whether or not these are adverse events. All findings whether related to an adverse event or part of each subject's medical history will be captured on the appropriate eCRF page.

A symptom-based physical examination will be performed at all other visits when necessary. If a subject reports any symptoms that requires additional physical examination besides the extra-intestinal manifestation (EIM) assessment, a symptom-based physical examination will be performed. The assessment of EIMs must be completed at all study visits. Please refer to Appendix C and Appendix E.

Height and Weight

For Subjects ≥ 18 years of age, height (with shoes off) will be measured at the Screening Visit of Study M14-234 Substudy 2 or Study M14-675. For subjects 16 or 17 years of age, where locally permitted, height (with shoes off) will be measured at the Screening Visit of Study M14-234 Substudy 2, Week 8, Week 16 and if continuing into Substudy 3 at Week 0 and Week 52/PD. Body weight will be measured at all scheduled visits. All measurements will be recorded in metric units where applicable.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, height and weight measurements may be performed by the subject or caregiver as needed.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at each visit. Blood pressure (BP), pulse rate and respiratory rate should be performed before blood draws are performed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

Chest X-Ray (CXR)

A CXR (posterior-anterior and lateral views) is required for all subjects at Screening to rule out the presence of TB or other clinically relevant findings (In Japan, a computed tomography [CT] scan of the chest may be performed in lieu of a CXR, at investigator's discretion). The CXR will not be required if the subject had a previous normal CXR

(posterior-anterior and lateral views) (or normal CT Scan of the chest for subjects in Japan) 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. The investigator may obtain a Baseline CXR if clinically indicated for a specific subject.

Subjects can have a repeat CXR anytime during the study as warranted based on the opinion of the investigator.

A CXR will be performed at Week 52/PD for subjects with a positive response to TB risk questionnaire Part 1 or for subjects with newly positive PPD and/or QuantiFERON-TB Gold Plus test after baseline.

A radiologist (or pulmonologist) must perform an assessment of the CXR (or CT Scan of the chest for subjects in Japan). The Principal Investigator or designee will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR (or CT Scan of the chest for subjects in Japan) for the presence of TB, the radiologist (or pulmonologist for subjects in Japan) and/or Principal Investigator (or designee) must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. In case of any abnormality indicative of active TB, the subject should not be enrolled into the study. If the CXR demonstrates changes suggestive or 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the absence of symptoms or positive medical history, if CXR cannot be done due to COVID-19 restrictions, the subject may continue in the study after discussion with TA MD. CXR should be performed as soon as restrictions allow at study site or local hospital/facility.

12-Lead Electrocardiogram (ECG)

For all subjects, a resting 12-lead ECG will be performed at Screening and Week 8/Premature Discontinuation Visit in Substudy 1 and 2 or Study M14-675; Week 16 of the Extended Treatment Period of Substudy 2 or Study M14-675, and at Week 52/Premature Discontinuation in Substudy 3. The ECG at Week 8 in Substudy 1, Substudy 2, or Study M14-675; or ECG at Week 16 of the Extended Treatment Period of Substudy 2 or Study M14-675 will serve as the baseline ECG for Substudy 3. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. If there are any findings that are clinically significant, the Principal Investigator must contact the TA MD before enrolling the subject. 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 kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol required documentation is available and provided nothing has changed in the subject's medical history to warrant a repeat test.

ECG should always be performed prior to obtaining blood samples. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

TB Testing/TB Prophylaxis

Screening

All subjects must be evaluated for TB at screening and annually unless the subject is considered to be TB test positive prior to screening. The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc. and it is the responsibility of the investigator to determine if a subject has prior, active or latent tuberculosis. Expert consultation for the evaluation and/or management of TB may be considered per Investigator discretion.

For all subjects, evidence of increased risk for TB will be assessed by a questionnaire (Appendix I) and tested for TB infection by QuantiFERON-TB Gold Plus test. The site staff will complete the TB risk assessment form in its entirety (Part 1 and Part 2) and enter the data into the appropriate eCRF. The TB risk assessment form will be completed annually (Part 1 only) for all subjects, regardless of TB test results. One or more "yes" response on the TB risk assessment form indicates increased risk of TB.

If a subject has a QuantiFERON-TB Gold Plus test within 90 days prior to Screening and source documentation is available, TB testing does not need to be performed by the central laboratory at Screening provided nothing has changed in the subject's medical history to warrant a repeat test. If a subject only has a negative PPD test within 90 days prior to Screening, a QuantiFERON-TB Gold Plus test is required at Screening. If the QuantiFERON-TB Gold Plus test cannot be performed by the central laboratory at Screening and source documentation is available the PPD Skin Test (also known as a TB Skin Test or Mantoux 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 a negative TB test and CXR not suggestive of active TB may 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.

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with no signs or symptoms and a CXR 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.

For subjects with a negative TB test result at Screening or the most recent evaluation, an annual TB follow-up test will be performed.

If an annual TB test is newly positive (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB, and subsequent annual TB follow-up tests are not required. Any positive TB test after the patient has started the study should be reported as an AE of latent TB or active TB (as applicable).

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant investigation and a repeat test before the next scheduled annual TB retest, the case (including the TB test results) should be discussed with the AbbVie TA MD.

TB Testing

The QuantiFERON-TB Gold Plus test (or equivalent) should be performed at Screening on all subjects. The PPD skin test should be utilized when the QuantiFERON-TB Gold Plus test (or equivalent) is not possible or if both tests are required per local guidelines.

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Plus Test and/or PPD Skin Test and/or history of latent or active TB. It is not required to repeat either test at Screening or during the study and should be considered positive.

- For regions that require both PPD and QuantiFERON-TB Gold Plus testing, both will be performed. If either PPD or QuantiFERON-TB Gold Plus is positive, the TB test is considered positive.
- If TB testing is done at Screening for subjects with a prior positive TB test and a positive result is reported, the subject is considered TB test positive.
- If TB testing is done for subjects with a prior positive TB test at the annual evaluation, repeated TB prophylaxis in not required for a positive result unless indicated by the subject's medical history.
- The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold Plus Test is not possible for any reason (unless both tests are required per local guidelines).
- If only a PPD is placed at screening, then the TB test to be used for the remainder of the study for that subject is the PPD. Similarly, if a subject enters the study with a QuantiFERON-TB Gold Plus test alone, then the subject should have their annual TB test performed with a QuantiFERON-TB Gold Plus test.
- If the QuantiFERON-TB Gold Plus Test is NOT possible (or if both the QuantiFERON-TB Gold Plus Test and the PPD are required per local guidelines) the PPD will be performed. The PPD 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 an ulcerating reaction to PPD in the past should not be re-exposed and the PPD should be considered positive.
- If the QuantiFERON-TB Gold Plus test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold Plus test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the patient is considered to be negative.

- Interpretation of a positive TB test in low risk subjects: In cases where the QuantiFERON-TB Gold Plus 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 Part I and Part II questions of the TB risk assessment questionnaire at Screening or Part I questionnaire annually) and has no clinical suspicion of TB, the investigator may perform a local QuantiFERON-TB Gold Plus test (or repeat testing 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 test to be negative based on his/her clinical judgment; if the repeat testing result is positive or indeterminate, the test is considered positive.
- An alternative IGRA (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold Plus.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the absence of symptoms or positive medical history, if QuantiFERON TB test or PPD cannot be done due to COVID-19 restrictions, the subject may continue in the study. QuantiFERON TB test or PPD should be performed as soon as restrictions allow at study site or local hospital/facility.

TB prophylaxis

At screening, if the subject has evidence of latent TB infection (no symptoms, positive TB test and the subject has a CXR not suggestive of active TB), prophylactic treatment must be initiated at least 2 weeks prior to administration of the study drug (or per local guidelines, whichever is longer). At least 6 months of prophylaxis need 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 can be considered.

In Ireland, the full course of prophylaxis treatment must be completed prior to the first dose of study drug.

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 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 prior to enrolling the subject.

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. Two to four weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms as well as laboratory assessment of toxicity to TB prophylaxis.

If the subject is experiencing signs of symptoms suspicious of 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.

Pregnancy Tests

A serum pregnancy test will be performed by the central lab at the Screening Visit on all female subjects of childbearing potential. 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. Where mandated by local requirements a negative serum pregnancy test will be required for subject enrollment.
- For subjects in Ireland and Argentina, a repeat serum pregnancy test ≥ 3 days later that is still borderline will result in screen failure. (A borderline serum pregnancy test may be repeated more than once during the screening period.)

Women of childbearing potential includes all women who are not surgically sterile (both ovaries and or both fallopian tubes removed or uterus removed) or post-menopausal (defined as at least 55 years of age with no menses for at least one year, without an alternate medical reason for amenorrhea, or less than 55 years of age with no menses for at least one year, without an alternate medical reason for amenorrhea and a FSH level > 40 IU/L).

In Substudy 1 and 2, women of childbearing potential will have a urine pregnancy test performed locally by designated study personnel at Baseline and all subsequent visits. In Substudy 3, women of childbearing potential will have a urine pregnancy test performed locally by designated study personnel at all visits and monthly at home between scheduled study visits. The results of the monthly at home tests will be communicated to the site by the subject and documented in the source documents.

Women of childbearing potential will also have a urine pregnancy test performed at home 30 days after the last visit. The results of follow up pregnancy test should be communicated during the telephone follow up call.

If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. If the serum pregnancy test is positive, dosing must be stopped and the subject must be discontinued from the study or, if pregnancy is identified at end of study visit, pregnancy must be reported to AbbVie as outlined in Section 6.1.6.

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

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 required.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Monthly urine pregnancy testing must be performed for women of child-bearing potential and results confirmed prior to administration of study drug to the subject. Urine pregnancy tests may be performed at the local lab 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)

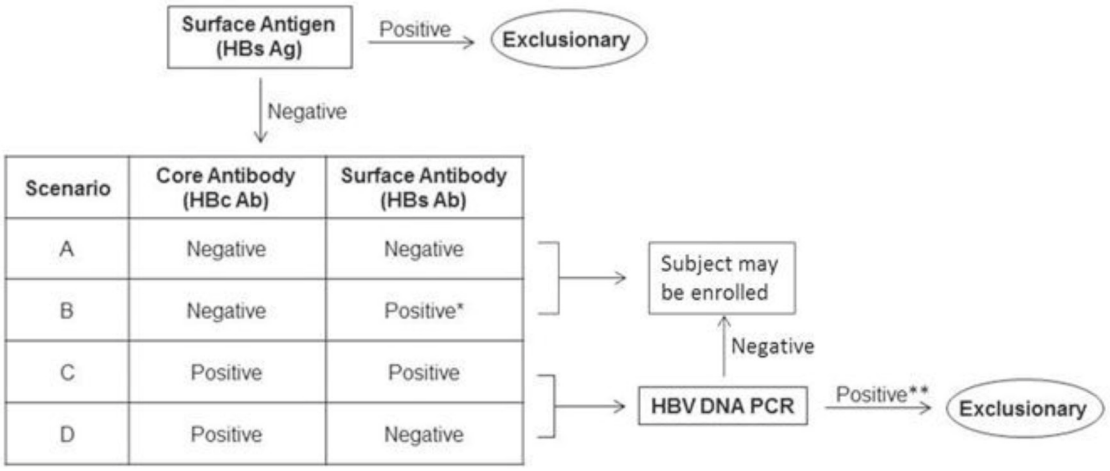
HBV serologic test results will be interpreted and managed as shown in Figure 4.

- 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.

Figure 4. Interpretation and Management of HBV Serologic Test Results



* 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.

** Where mandated by local requirements; subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed approximately 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+ and HBc Ab–. If necessary, HBV DNA PCR may be tested at unscheduled visits.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that the HBV DNA PCR cannot be performed for subjects who require the test due to study modifications related to the COVID-19 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) are excluded from study participation. An anti-HIV antibody (Ab) test 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

Blood samples will be obtained for the laboratory tests listed in Table 1. Tests should always be performed only after all clinical assessments, questionnaires (Inflammatory Bowel Disease Questionnaire [IBDQ], etc.) and vital sign determinations are obtained during a visit.

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

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

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

Urinalysis

Urine samples will be obtained and sent to the central laboratory for the tests listed in Table 1. Microscopic urinalysis will only be performed by the central laboratory if the dipstick UA results are abnormal, where abnormal is defined as leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace. Sites will not be provided with urinalysis dipsticks.

Other Laboratory Assessments

High Sensitivity C-Reactive Protein

Blood samples for high-sensitivity C-reactive protein (hs-CRP) will be obtained. Blood draws should be performed after all clinical assessments, questionnaires (IBDQ, etc.), and vital sign determinations are obtained. The hs-CRP test will be performed by the Central Lab for all subjects as indicated in Appendix C and Appendix E. The results will be blinded to the sponsor, investigator, study site personnel, and the subject. Local laboratory or site testing for CRP is not allowed after Baseline with the exception when the subject has a medical condition in which CRP level is deemed to be necessary for the diagnosis and treatment in Investigator's discretion and **after** consulting with the AbbVie TA MD. For future data assessments, it may be required to unblind the CRP data in an interim interval.

Lymphocyte Subsets (TBNK)

Blood samples will be collected at Baseline, Week 8 and Premature Discontinuation in Substudy 1 or in Substudy 2 and at Week 16/Premature Discontinuation of the Extended Treatment Period of Substudy 2 to assess the effects of upadacitinib inhibition on lymphocyte subsets: T (CD4+ and CD8+) cells, B (CD19+) cells, natural killer (NK) cells, and natural killer T (NKT) cells. These tests will be performed by the Central Lab.

Table 1. Clinical Laboratory Tests

<table>
<tr><th>Hematology</th><th>Clinical Chemistry[a]</th><th>Urinalysis[b]</th></tr>
<tr><td rowspan="3">Hematocrit
Hemoglobin
Red Blood Cell (RBC) count
Reticulocyte count
White Blood Cell (WBC) count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count</td><td rowspan="2">Blood Urea Nitrogen (BUN)
Creatinine
Total bilirubin
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Alkaline phosphatase
Creatine phosphokinase (CPK)
Sodium
Potassium
Chloride
Bicarbonate
Calcium
Inorganic phosphorus
Uric acid
Total protein
Albumin
Glucose
Gamma glutamyl transferase (GGT)
Lipid Test:
Cholesterol
LDL-C
HDL-C
Triglycerides</td><td>Specific gravity
Ketones
pH
Protein
Glucose
Blood
Nitrite
Bilirubin
Urobilinogen
Leukocytes
Microscopic Examination</td></tr>
<tr><td>Other Laboratory Tests</td></tr>
<tr><td>Stool Samples Collected</td><td rowspan="2">Serum pregnancy test
Urine pregnancy test
High sensitivity C-reactive protein (hs-CRP)
Hepatitis B Surface Antigen
Hepatitis B Surface Ab
Hepatitis B Core Ab
Hepatitis B Core Ab Immunoglobulin M (IgM)
Hepatitis C Ab Screen
HBV DNA PCR reflex only
HCV RNA reflex only
QuantiFERON-TB Gold Plus
Pharmacokinetic
eGFR
Lymphocyte Subsets (TBNK Panel)[c]
HIV Ab
Beta-D-Glucan (Japan only)</td></tr>
<tr><td>C. difficile toxin
Fecal calprotectin</td></tr>
<tr><td colspan="3">Additional Samples Collected (Optional)</td></tr>
<tr><td colspan="3">Blood, serum, plasma, stool and intestinal tissue samples for exploratory research, validation studies[d] and biologic drug level.[e]</td></tr>
</table>

a. Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

b. The Central Laboratory will perform the urinalysis. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace. Sites will not be provided with urinalysis dipsticks.

Table 1. Clinical Laboratory Tests (Continued)

c. Lymphocyte subsets include T (CD4+ and CD8+) cells, B (CD19+) cells, natural killer (NK) cells, and natural killer-T (NKT) cells.
d. Preferably collected while subjects are in a fasting condition.
e. 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 or later from the last dose; (2) adalimumab, certolizumab, golimumab, or vedolizumab: may be tested approximately 6 weeks or later from the last dose; (3) ustekinumab: may be tested approximately 8 weeks or later from the last dose.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. It is recommended to perform all scheduled tests in the protocol, except for hs-CRP, Fecal calprotectin, PK, and optional samples for exploratory research which should not be collected. For hs-CRP local testing can only be performed if deemed to be necessary by the investigator after discussion with TA MD.

Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. The results should be reviewed by the investigator and documented in EDC as an unscheduled lab as soon as possible.

If it is not possible to perform all the tests, the tests in the below table should be performed at minimum for safety evaluation.

Hematology	Clinical Chemistry	Urine	Tuberculosis tests*
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	QuantiFERON TB test or PPD (Study M14-234 SS3 and Study M14-533) Chest X-Ray (Study M14-234 SS3 and Study M14-533)

* TB Test and Chest X-Rays to be completed only at the required visits per protocol.

If laboratory samples cannot be obtained, study drug administration may be continued provided that the following criteria are met:

During Substudy 2 drug may be dispensed if:

1. There is at least 1 post-Baseline lab assessment (either Week 2 or Week 4 visit)

   AND

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

   AND

3. No longer than 4 weeks have passed from the last safety lab tests.

During Substudy 3 drug may be dispensed if the following criteria are met:

1. There is at least 1 post-Week 0 lab assessment

   AND

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

AND

3. No longer than 12 weeks have passed from the last safety lab tests.

Stool Samples Collected

Fecal Calprotectin

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

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

All stool samples should be collected before any bowel preparation for endoscopy is started. The central laboratory will be utilized to process and provide results for these laboratory tests. For future data assessments, it may be required to unblind the CRP data in an interim interval.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If subject is unable to attend visit where fecal calprotectin stool samples are collected, these should not be collected at a local lab.

C. Difficile

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

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

Subjects who are positive for *C. difficile* toxin should be screen-failed; these subjects may be re-screened after completing the appropriate treatment. For subjects who are borderline for *C. difficile* toxin, the investigator may send another sample for test. If the result is negative, the investigator may consider the test to be negative based on his/her judgment. If the result is positive or borderline, the test is considered positive and subject should be screen failed. For those subjects with two borderline results, the PI can decide if *C.difficile* treatment is needed based on his/her clinical judgment; these subjects may be re-screened with or without *C. difficle* treatment.

Outcomes and Questionnaires

The following outcomes and questionnaires will be completed at the time points indicated in Appendix C and Appendix E. However, please ensure questionnaires are always completed prior to obtaining blood samples. Refer to Appendix G for descriptions of Patient Reported Outcomes (PRO).

- IBDQ – Inflammatory Bowel Disease Questionnaire
- SF-36 – Short Form 36
- EQ-5D-5L – European Quality of Life 5 Dimensions 5 Levels
- FACIT-F – Functional Assessment of Chronic Illness Therapy-Fatigue
- WPAI – Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis
- PGIC – Patient Global Impression of Change
- PGIS – Patient Global Impression of Severity (only in select sites and not in Substudy 1)
- UC-SQ – Ulcerative Colitis Symptoms Questionnaire
- HCRU – Supplemental Hospitalization and Surgery forms

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference, except baseline. All PROs, except EQ-5D-5L scale, are eligible for

completion by interview. If there are time constraints to the phone visit, at a minimum, the following PROs must be completed:

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Patient Global Impression of Change (PGIC)
- Patient Global Impression of Severity (PGIS)

Prior to conducting any phone/video visits to obtain PRO data 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 over the phone. The date and start and stop time of PRO data collection should be recorded along with who collected the information, their role and which questionnaires were completed.

Corticosteroid Taper

At Baseline of Substudy 3 (Week 8 or Week 16), subjects who are taking corticosteroid therapy at Baseline of Substudy 1 or 2 or Study M14-675 will have their corticosteroid dose tapered according to the following proposed schedule or based on investigators' discretion:

Table 2. Corticosteroid Dose Taper

	Dose	Rate
Oral Prednisone (or equivalent)	> 10 mg/day ≤ 10 mg/day	5 mg/day/week 2.5 mg/day/week
Oral Budesonide	≤ 9 mg/day	3 mg/day/week
Oral budesonide-MMX (e.g., Cortiment, eUceris)		Discontinue
Oral beclomethasone		Discontinue

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

Subject Diary

Subjects will be dispensed an electronic diary (eDiary) at Screening in Study M14-234 or Study M14-675 and the site staff will enter the NORMAL baseline number of stools in a 24-hour period when the subject's UC is **not** active to allow for scores to be calculated.

Subjects 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. If subjects require re-training during the study, the site staff will accommodate this requirement.

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 as the diary data required to be entered by the subject(s) cannot be changed or altered in any way.

Study Drug Dispensing/Administration

Study drug will be dispensed to subjects at the time points indicated in Appendix C and Appendix E. No study medication will be dispensed at Week 52 in Substudy 3.

Study drug will be taken orally once daily beginning at the Baseline Visit and should be taken at approximately the same time each day. At scheduled visits, study drug should be administered after all assessments and examinations scheduled for that day have been completed if the visit occurs at the time the subject is taking study drug each day. If study drug is being taken earlier than when the visit is set to occur, the time of the last 2 doses will be documented in the eCRF and pharmacokinetic (PK) samples drawn at the visit.

Refer to Section 5.5 for additional information.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Study drug may be only dispensed to subjects if specific Laboratory result criteria are met; please see these outlined below and refer to the Clinical Laboratory Tests section above for more information.

If laboratory samples cannot be obtained, study drug administration may be continued provided that the following criteria are met:

During Substudy 2 study drug may be dispensed if:

1. There is at least 1 post-Baseline lab assessment (either Week 2 or Week 4 visit)

   AND

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

   AND

3. No longer than 4 weeks have passed from the last safety lab tests.

During Substudy 3 drug may be dispensed if the following criteria are met:

1. There is at least 1 post-Week 0 lab assessment

   AND

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

   AND

3. No longer than 12 weeks have passed from the last safety lab tests.

Study drug may be shipped from the study site directly to the study subject's home if all 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., drug dosing diaries, paper copies of PROs). 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 COVID-19 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.

DTP study drug shipment will be allowed on the study for the duration of the COVID-19 pandemic and will be removed once the pandemic is considered to be resolved.

Mayo Score/Partial Mayo Score

Data from the subject diaries will be collected in order to calculate Mayo score/Partial Mayo score at the time points indicated in Appendix C and Appendix E.

Whenever possible, the same physician (investigator or sub-investigator) should determine the Physician's Global Assessment (PGA) subscore for an individual subject through the duration for the study. The directions for capturing the SFS, RBS, and PGA subscores of the Mayo score are described in Appendix H.

Diary entries from the most recent 3 consecutive days prior to the visit should be utilized for calculation purposes. If diary entries from the 3 most recent consecutive days prior to the visit are not available, the 3 most recent consecutive days in the last 10 days will be utilized. If data are not available for 3 consecutive days, the average of the entries from the most recent 3 non-consecutive days in the last 10 days will be utilized.

Endoscopy

All endoscopies should be recorded in a color video format at the time points noted in Appendix C and Appendix E. There will be a window of 7 days prior to the scheduled visit to conduct the endoscopy. For the screening endoscopy, this procedure may be completed at any time during the Screening Period but not on the date the subject is randomized as the central reader review of the endoscopy video is required for study entry (central reading can take up to 3 business days). For other scheduled visits, the endoscopy may not occur after the visit, only on the day of or in advance of the scheduled visit. 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).

Endoscopies will be reviewed by a primary central reader who is blinded to the subject's clinical data, the site's endoscopy assessment and the subject's therapy. If, in the assessment of the endoscopist at the site, the Screening endoscopy shows a normal colonic mucosa, the subject should be screen-failed and the video should not be sent for central reading. The endoscopy will be used for calculation of the endoscopy subscore of the Mayo score. The endoscopy subscore will be documented by the endoscopist at the site and maintained in the subject's source documents. In addition to endoscopic evaluation using Mayo endoscopic sub-score, the endoscopy findings using the UCEIS scoring system will be used for additional exploratory analyses. During all endoscopy procedures, the endoscopist at the site should determine the segment where there is a clear demarcation between normal and inflamed mucosa and document the distance from the anal verge (in centimeters) in the eCRF.

Screening Endoscopy: A full colonoscopy will be performed at Screening. The endoscopy subscore result from the central reader will be entered into the eCRF by the site and used to evaluate the eligibility of a subject at Baseline for the study. The central reader's assessment will be used in the Mayo score calculations for all efficacy endpoint assessments.

Week 8 (Substudies 1 and 2), Week 16 (Substudy 2), and Week 44 in Substudy 3 (for subjects entering from Substudy 1), or **Week 52/PD (Substudy 3) Endoscopy:** The Week 8 and Week 52/PD endoscopies may be either a full colonoscopy or a flexible sigmoidoscopy depending on the extent of the disease at Screening Endoscopy should be performed up to the segment where a clear demarcation of inflammation is observed. For subjects that entered Substudy 2 Part 2, an endoscopy will be performed at Week 16. A flexible sigmoidoscopy is recommended at Week 16; however, the use of a flexible sigmoidoscopy or colonoscopy will be based on the investigator's discretion per local practice. The site's endoscopist scoring will be entered into the eCRF by the site and used for the Mayo score calculation for the purposes of re-randomization into Substudy 3. For

the Week 8 or Week 16 re-randomization, the local reading will be compared with the baseline central reading in order to determine clinical response status. For subjects that reach and complete the Week 52 endoscopy for Substudy 3 of Study M14-234, the local endoscopy reading will be utilized to determine the status of clinical remission for the purpose of treatment assignment in Study M14-533. The central reader's assessment will be used for the Mayo scores used in all efficacy endpoint assessments. For subjects who discontinue during the maintenance period (Substudy 3), an endoscopy will not be performed if the subject discontinues the study prior to the Week 28 Visit.

The same endoscopist should, where possible, perform all endoscopies for an individual subject throughout the study. In addition, where possible, the investigator or subinvestigator should be the endoscopist for the study. The endoscopy subscores by segment will be noted in the subject's source documents and in the database but the central reader's endoscopy subscore will be used for the efficacy analyses.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If an Endoscopy required at Substudy 2 Week 8 and Week 16 is not able to be scheduled at the study site in the required protocol window due to COVID-19, then this may be performed ± 7 days from the planned visit and can be completed at a different hospital/facility.

If an Endoscopy required at Substudy 3 Week 52 is not able to be scheduled at the study site in the required protocol window due to COVID-19, then this may be performed –2 weeks and +4 weeks from the planned visit and can be completed at a different hospital/facility. The investigator should evaluate the benefits-risks for continuing the subject in the study before the division of window extension.

If the endoscopy cannot be performed during this extended window at the site or another location, please refer to the guidance for subjects outlined in Section 5.1.2.

Biopsy During Endoscopy

Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available a diagnostic biopsy from the most affected observed area of the colon must be performed during the Screening endoscopy and read by a qualified local pathologist and the results reviewed by the investigator, the central laboratory will not provide a pathology report during the screening endoscopy to document UC diagnosis. 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.

Biopsies sent to the central laboratory will not be returned to sites and will be retained for study use only.

Obtainment of biopsy samples should also be recorded on the video.

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 the Screening endoscopy. 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.

During all endoscopies up to 3 sets of biopsies are to be collected; one mandatory set of biopsies and, if consented for, two optional sets of biopsies. Each set of biopsies should consist of 2 samples each, obtained from the rectosigmoid colon (approximately 15 –

30 cm from the anal verge) for histologic assessment. For each set of 2 samples, one should be taken from the area of most inflammation (if the area is ulcerated, the sample should be obtained from the edge of the ulcer), and one from an area that is representative of the general degree of mucosal inflammation present in that segment. For all histology biopsies, the location of the biopsy specimen (distance from the anal margin) should be recorded.

For China only: only a single biopsy at each endoscopy from the most inflamed area (HistoMOST) will be required per local requirements. The single, required biopsy will be taken from the area of most inflammation (if the area is ulcerated, the sample should be obtained from the edge of the ulcer) for histologic assessment at each required timepoint as per Appendix C.

For follow-up endoscopies, in the absence of any visible lesions or areas of general inflammation characteristic of UC, up to 3 sets of biopsies should be collected from normal mucosa in the same segments as noted above.

Biopsy Sample Collection, Storage and Shipping:

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

Biopsy specimens per subject should be obtained by endoscopy for histologic assessment at the time points indicated in Appendix C and Appendix E. Using routine forceps for tissue collection, obtain the required number of biopsy specimens and process the specimens following the instructions in the study-specific laboratory manual.

Intestinal Tissue Analysis

The following analyses will be sent to the central laboratory and performed on tissue samples:

1. Qualitative UC histological assessment using Geboes histologic activity score,[25] and other histologic scoring systems. These samples may not be read in real time, however if unexpected findings, such as dysplasia, are noted on the histology biopsies, the central laboratory will contact the investigator to inform him/her about the unexpected finding. Subjects who are found to have high grade colonic dysplasia on the submitted biopsy will be terminated from the trial at the time the dysplasia is discovered. Unexpected findings should be recorded as an adverse event.
2. Subjects will have the option to provide tissue biopsies (per local requirements) for future exploratory research and/or validation studies. For more information, please refer to Section 5.3.1.2.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Biopsy completion should follow the endoscopy guidance if the visit is affected by COVID-19. If an endoscopy is completed at an alternative location from the study site the study required biopsy is not required. Biopsy can be completed per endoscopist's discretion for local evaluation.

Follow-Up Period

Subjects will be contacted approximately 30 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs).

During this follow-up call the results of the follow-up at home pregnancy test should be communicated to the site and follow reporting found in Section 6.1.6.

Subjects may discontinue study drug treatment at any time during study participation. Subjects that end study participation early will have a Premature Discontinuation Visit and complete the procedures outlined for the PD Visit in Appendix C through Appendix F as soon as possible after the last dose of study drug and preferably prior to the administration of any new therapies.

Unscheduled Visits

An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples will be obtained for the laboratory tests listed in Table 1, 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.

Home Healthcare Service Due to COVID-19 Pandemic

Subjects may be offered the option of home healthcare visits provided by a licensed health care provider, such as a study nurse or third-party vendor. Study procedures conducted in the home setting may include physical examination, vital signs, collection of laboratory tests and Patient Reported Outcomes. This option can only be offered in countries and sites that comply with local regulatory and IRB/IEC requirements for homecare.

Finally, it is recommended that medical personnel entering a subject's home adhere to local health regulations during the COVID-19 pandemic, such as the use of Personal Protective Equipment (PPE), as required.

Protocol deviations must be recorded per AbbVie's standard process.

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.

Individuals performing home visits need to be added to the delegation log.

5.3.1.2 Collection and Handling of Optional Samples for Exploratory Research and Validation Studies

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

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

Validation studies, including those related to the development of potential in vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

AbbVie (or people or companies working with AbbVie) will store the biomarker exploratory research/validation studies 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 UC and related conditions continues, but for no longer than 20 years after study completion.

The following samples will be collected according to Appendix D and Appendix F from each subject who consents to provide samples for exploratory research/validation studies:

- Blood samples for pharmacogenetic and epigenetic analyses (DNA)
- Blood samples for transcriptomic and/or epigenetic analyses (RNA) [if possible, subjects should be fasted for approximately 8 hours prior to collection]

- Serum and plasma samples for systemic analyses including, but not limited to, proteomics and metabolomics (if possible, subjects should be fasted for approximately 8 hours prior to collection)
- Stool for biomarker analysis
- Rectosigmoid biopsy for exploratory research (frozen) and transcriptomic and/or epigenetic analysis (RNAlater).

Samples will be shipped to AbbVie or a designated laboratory for DNA/RNA extraction, if applicable, and/or analyses or long-term storage. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If subject is unable to attend visit where optional exploratory samples are collected, these should not be collected at a local lab.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetics assay of upadacitinib and possibly other concomitant medications will be collected at the following times:

- Substudy 1: Week 2, Week 4, Week 6, and Week 8/PD
- Substudy 2 Part 1: Week 2, Week 6, and Week 8/PD
- Substudy 3: Week 36 and Week 52/PD

On visits where the blood samples for assay of upadacitinib are being collected as noted, samples should be collected prior to dosing and the subjects should take the study drug dose at the clinic after collecting the PK blood sample, when possible. However, if the subject normally takes the study drug dose at a time that is much earlier or after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample will be collected at any time during the visit.

The date and accurate time of the PK sample collection and the last two study drug doses will be recorded on the applicable requisition forms and in the eCRF to the nearest minute.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If subject is unable to attend visit where pharmacokinetic samples are collected, these should not be collected at a local lab.

5.3.2.2 Handling/Processing of Samples

The blood samples for upadacitinib assays will be labeled with the type of sample, the protocol number, the subject number, and the visit week. Additional detailed instructions for the handling and processing of samples will be provided from the Central Lab.

5.3.2.3 Disposition of Samples

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

5.3.2.4 Measurement Methods

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.

5.3.3 Efficacy Variables

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

Clinical Remission:

- Per Adapted Mayo: SFS ≤ 1 and not greater than baseline, RBS of 0, and endoscopic subscore ≤ 1 (*note:* evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2).
- Per Full Mayo: Full Mayo score of ≤ 2 with no subscore > 1

Clinical Response:

- Per Adapted Mayo: decrease from baseline in Adapted Mayo score ≥ 2 points and ≥ 30%, accompanied by a decrease in RBS of ≥ 1 or an absolute RBS of 0 or 1
- Per Full Mayo: decrease from baseline in Full Mayo score ≥ 3 points and ≥ 30%, accompanied by a decrease in RBS of ≥ 1 or an absolute RBS of 0 or 1
- Per Partial Adapted Mayo: decrease from Baseline ≥ 1 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Endoscopic remission: Endoscopic subscore of 0

Endoscopic improvement: Endoscopic subscore ≤ 1

Histologic improvement: Decrease from Baseline in Geboes score

Histologic-endoscopic mucosal improvement: Endoscopic subscore ≤ 1 and Geboes score ≤ 3.1

Mucosal healing: Endoscopic score = 0 and Geboes score < 2

5.3.3.1 Primary Variables

The primary endpoint for Phase 2b Induction (Substudy 1) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (defined as SFS ≤ 1, RBS of 0, and endoscopic subscore ≤ 1) at Week 8.

The primary endpoint for Phase 3 Induction (Substudy 2) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (defined as SFS ≤ 1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤ 1) at Week 8. *Note:* in Substudy 2, evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

The primary endpoint for Phase 3 maintenance (Substudy 3) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (definition same as definition in Substudy 2) at Week 52.

5.3.3.2 Secondary Variables

Ranked secondary efficacy variables for Phase 2b induction (Substudy 1) are as follows:

1. Proportion of subjects with endoscopic improvement (defined as an endoscopic subscore ≤ 1) at Week 8
2. Proportion of subjects achieving clinical remission per Full Mayo score (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8
3. Proportion of subjects achieving clinical response per Adapted Mayo score (defined as decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1) at Week 8
4. Proportion of subjects achieving clinical response per Partial Mayo score (using the Mayo Scoring System for Assessment of Ulcerative Colitis Activity, excluding endoscopic subscore; clinical response defined as decrease from baseline in the

Partial Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1) at Week 2

5. Change in Full Mayo score from Baseline to Week 8
6. Proportion of subjects with endoscopic remission (defined as an endoscopic subscore of 0) at Week 8
7. Proportion of subjects who achieved histologic improvement (defined as decrease from baseline in Geboes score) at Week 8

Ranked secondary efficacy variables for Phase 3 induction (Substudy 2) are as follows:

1. Proportion of subjects with endoscopic improvement at Week 8
2. Proportion of subjects with endoscopic remission at Week 8
3. Proportion of subjects achieving clinical response per Adapted Mayo Score at Week 8
4. Proportion of subjects achieving clinical response per Partial Adapted Mayo score (defined as decrease from Baseline ≥ 1 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at Week 2
5. Proportion of subjects achieving histologic-endoscopic mucosal improvement at Week 8
6. Proportion of subjects who reported no bowel urgency at Week 8
7. Proportion of subjects who reported no abdominal pain at Week 8
8. Proportion of subjects who achieved histologic improvement at Week 8
9. Change from Baseline in IBDQ total score at Week 8
10. Proportion of subjects with mucosal healing at Week 8
11. Change from Baseline in FACIT-F score at Week 8

Ranked secondary efficacy variables for Phase 3 Maintenance (Substudy 3) are as follows at Week 52 (for subjects who enrolled under the protocol with 44-week maintenance period, these will apply at Week 44, as applicable):

1. Proportion of subjects with endoscopic improvement
2. Proportion of subjects who maintain clinical remission per Adapted Mayo score among subjects who achieved clinical remission per Adapted Mayo score in Study M14-234 (Substudy 1 or 2) or Study M14-675
3. Propotion of subjects who achieved clinical remission at Week 52 per adapted Mayo score and were corticosteroid free for ≥ 90 days among subjects in clinical remission in the end of the induction treatment in Study M14-234 (Substudy 1 or 2) or Study M14-675.
4. Proportion of subjects with endoscopic improvement among subjects with endoscopic improvement in Study M14-234 (Substudy 1 or 2) or Study M14-675
5. Proportion of subjects with endoscopic remission
6. Proportion of subjects maintain clinical response per Adapted Mayo score
7. Proportion of subjects with histologic-endoscopic mucosal improvement
8. Change from Baseline in IBDQ total score
9. Proportion of subjects with mucosal healing
10. Proportion of subjects who reported no bowel urgency
11. Proportion of subjects who reported no abdominal pain
12. Change from Baseline in FACIT-F score

5.3.3.3 Additional Variables

In Substudies 1 and 2, additional efficacy variables are as follows and will be evaluated.

- Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 6) at Week 8
- Proportion of subjects with UC-related hospitalizations through Week 8
- Proportion of subjects with UC-related surgeries through Week 8
- Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 8
- Proportion of subjects with SFS of 0, RBS of 0 and endoscopic subscore of 0 at Week 8
- Proportion of subjects with SFS of 0, RBS of 0 and endoscopic subscore of ≤ 1 at Week 8
- Proportion of subjects achieving clinical remission per Full Mayo Score (defined as a full Mayo score ≤ 2 with no sub-score > 1) at Week 8
- Change in Full Mayo Score from Baseline to Week 8
- Proportion of subjects achieving clinical remission per Partial Mayo score over time.
- Proportion of subjects achieving clinical response per Partial Adapted Mayo score over time
- Proportion of subjects achieving clinical response per Partial Mayo score over time.
- Proportion of subjects with SFS ≤ 1 over time.
- Proportion of subjects with RBS = 0 over time.
- Proportion of subjects with SFS ≤ 1 at Week 2.
- Proportion of subjects with RBS of 0 at Week 2.
- Proportion of subjects with fecal calprotectin below 150 mg/kg over time.
- Change from Baseline in fecal calprotectin over time
- Change from Baseline in hs-CRP over time.
- Change from Baseline in Partial Adapted Mayo score, Partial Mayo score and SFS, RBS over time.
- Change from Baseline in UCEIS score over time.

- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in IBDQ total and domain score over time.
- Change from Baseline in individual IBDQ item under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29) over time.
- Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) over time.
- Proportion of subjects with IBDQ remission (IBDQ total score ≥ 170) over time.
- Change from Baseline in EQ-5D-5L score over time.
- Change from Baseline in WPAI scores over time.
- Change from Baseline in SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) components and domain scores over time.
- Proportion of subjects by PGIC category over time.
- Proportion of subjects by PGIS category over time.
- Change from Baseline in FACIT-F score over time.
- Change from Baseline in UC-SQ score over time
- Proportion of subjects with all cause hospitalization through Week 8
- Proportion of subjects with all cause surgery through Week 8

In Substudy 3, additional efficacy variables are as follows and will be evaluated:

- Proportion of subjects who discontinued corticosteroid use, remained corticosteroid free for ≥ 90 days immediately before Week 52 and achieved clinical remission per Adapted Mayo score in subjects taking steroids at Baseline (of induction)
- Proportion of subjects achieving response in IBDQ Bowel Symptom domain at Week 52 (increase of IBDQ bowel symptom domain score ≥ 6)

- Proportion of subjects achieving response in IBDQ fatigue item at Week 52 (increase of IBDQ fatigue item score ≥ 1)
- Proportion of subjects who are taking corticosteroids at Baseline (of induction) and are steroid-free over time.
- Proportion of subjects who are taking corticosteroid at Baseline (of induction) and are steroid free at Week 52
- Proportion of subjects who discontinued corticosteroid use and achieved clinical remission per Adapted Mayo score at Week 52 in subjects taking steroids at Baseline (of induction)
- Proportion of subjects achieving clinical remission per Full Mayo Score (defined as a full Mayo score ≤ 2 with no sub-score > 1) at Week 52
- Proportion of subjects who discontinued corticosteroid use and achieved clinical remission per Partial Mayo Score over time in subjects taking steroids at baseline (of induction)
- Proportion of subjects who discontinued corticosteroid use of ≥ 90 days immediately before Week 52 and achieved clinical remission at Weeks 0 and Week 52 of Substudy 3, in subjects who were taking steroids at Baseline (of induction)
- Proportion of subjects who discontinued corticosteroid use of ≥ 90 days immediately before Week 52 and achieved a SFS ≤ 1 (and not worse than Baseline of induction) and RBS = 1 at Weeks 36 and 44 and clinical remission at Week 52, in subjects who were taking steroids at baseline (of induction)
- Proportion of subjects achieving clinical remission per Partial Mayo score over time.
- Proportion of subjects with SFS of 0, RBS of 0 and endoscopic subscore of 0 at Week 52
- Proportion of subjects with SFS of 0, RBS of 0 and endoscopic subscore of ≤ 1 at Week 52
- Proportion of subjects with SFS ≤ 1, RBS = 0 at Week 28 and clinical remission per adapted Mayo score at Week 52
- Proportion of subjects with SFS ≤ 1, RBS = 0 at Week 28 and Week 52

- Proportion of subjects with SFS of 0, RBS of 0, and endoscopic subscore of 0 over time.
- Proportion of subjects achieving clinical response per Partial Mayo score over time.
- Proportion of subjects with SFS ≤ 1 over time.
- Proportion of subjects with RBS of 0 over time.
- Proportion of subjects with fecal calprotectin below 150 mg/kg over time.
- Change from Baseline in hs-CRP over time.
- Change from Baseline in fecal calprotectin over time
- Change from Baseline in corticosteroid dose over time.
- Change from Baseline in Adapted Mayo score, Partial Adapted Mayo score, Full Mayo score, Partial Mayo score and Mayo subscores over time.
- Change from Baseline in UCEIS score over time.
- Proportion of subjects with histologic improvement at Week 52
- Proportion of subjects with histologic remission at Week 52
- Proportion of subjects with histologic remission (defined as Geboes score < 2) at Weeks 8, or Week 16, and Week 52.
- Change from Baseline in histologic score over time.
- Change from Baseline in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight).
- Change from Baseline in subject-reported stool frequency (absolute values).
- Change from Baseline in IBDQ total and domain score over time.
- Change from Baseline in individual IBDQ item under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29) over time.
- Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) over time.
- Proportion of subjects with IBDQ remission (IBDQ total score ≥ 170) over time.
- Change from Baseline in EQ-5D-5L score over time.

- Change from Baseline in WPAI scores over time.
- Change from Baseline in SF-36 PCS, MCS components and domain scores over time.
- Proportion of subjects by PGIC category over time.
- Proportion of subjects by PGIS category over time.
- Change from Baseline in UC-SQ score over time.
- Health care resource utilization (all-cause and UC-related hospitalizations and surgeries) during the study.
- Incidence rate of UC-related hospitalizations.
- Incidence rate of UC-related surgeries.

In addition, change from Week 0 of Substudy 3 will be summarized for hs-CRP, fecal calprotectin, IBDQ total and domain score, EQ-5D-5L score, FACIT-F score, and other PRO endpoints, as applicable.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Plasma upadacitinib concentrations will be obtained at the times indicated in Appendix C and Appendix E. A non-linear mixed-effect modeling approach will be used to estimate the population central value 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 Exploratory Research Variables and Validation Studies

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.

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

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

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol. Toxicity management criteria for events of serious infections, malignancy, cardiovascular events, gastrointestinal perforation, ECG abnormality, and select laboratory abnormalities are described in Section 6.1.7 Toxicity Management.

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

- Clinically significant abnormal laboratory results or adverse events, which rule out continuation of the study medication, as determined by the investigator and the AbbVie TA MD.
- The investigator believes it is in the best interest of the subject.

- The subject requests withdrawal from study drug or the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie 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 medication.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by investigator or the AbbVie TA MD.
- Serious infections (e.g., sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk for continuation of the study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix
- Subject develops a gastrointestinal perforation (other than appendicitis or mechnical injury)
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits as outlined in the Study Activities daily, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation Visit must be completed as soon as possible, preferably within 2 weeks.

A final telephone visit will occur for all subjects, approximately 30 days after the last dose of study medication to determine the status of any ongoing AEs/serious AEs (SAEs) or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last study drug dose and the primary reason for premature discontinuation 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 the 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.

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 attempted and one certified letter must be sent and documented in the subject's source documentation.

Subjects who discontinue the study prematurely will not be replaced.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in Section 5.3.1.1 and Appendix C and Appendix E.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Refer to the Section 5.3.1.1 and Appendix C and Appendix E for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

For subjects with signs and/or symptoms and suspicion of COVID-19 or if a diagnosis has been confirmed, study drug should not be administered until the infection has resolved or coronavirus infection has been ruled out. There are no time limits for study drug interruption as long as no permanent study discontinuation criteria have been met. The investigator should contact the TA MD before reintroducing study drug in subjects who were infected with COVID-19. The study drug interruption should be captured on related CRFs with reasons due to COVID-19.

For subjects who are asymptomatic and had primary exposure to COVID-19 (e.g., family member tests positive) or have concerns about taking upadacitinib with ongoing COVID-19 transmission the investigator can decide to continue or interrupt study drug on a case-by-case basis taking into account the risk:benefit of continuing study drug. The investigator can temporarily interrupt study drug at any time for a safety issue, or for any reason if they feel that the risk outweighs the benefit of study treatment.

5.4.2 Discontinuation of Entire Study

The study will be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

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

notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

Study drug will be taken orally once daily beginning at the Baseline Visit and should be taken at approximately the same time each day. The study drug can be taken with or without food.

5.5.1 Treatments Administered

In Substudy 1, subjects were assigned to 1 of 5 groups and received 2 tablets of study drug QD as shown in Table 3. In Substudy 2, all subjects will receive 1 tablet QD. In Part 1 of Substudy 2, subjects will be assigned to 1 of 2 groups and will receive 1 tablet of upadacitinib 45 mg QD or matching placebo QD, while in Part 2 of Substudy 2, subjects will receive 1 tablet open-label upadacitinib 45 mg QD as shown in Table 3.

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, 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. Refer to see Section 5.3.1.1 for details on DTP shipment of study drug.

DTP study drug shipment will be allowed on the study for the duration of the COVID-19 pandemic and will be removed once the pandemic is considered to be resolved.

For subjects from Study M14-234 Substudy 2 and Study M14-675:

- Subjects from Study M14-234 Substudy 2 Part 1 and Study M14-675 Part 1 who received upadacitinib 45 mg and achieved clinical response will be re-randomized to 1 of 3 groups in Cohort 1 (upadacitinib 15 mg, 30 mg or placebo) and will receive 1 tablet of study drug QD. Subjects from Study M14-234 Substudy 2 Part 2 and Study M14-675 Part 2 who received placebo in Part 1 and upadacitinib in Part 2 and achieved clinical response will be re-

randomized to 1 of the 3 groups in Cohort 1 and will receive 1 tablet of study drug QD

- Subjects from Study M14-234 Substudy 2 part 1 and Study M14-675 Part 1 who received placebo and achieved clinical response will continue to receive placebo in Cohort 2.
- Subject from Study M14-234 Substudy 2 Part 2 and Study M14-675 Part 2 who received upadacitinib in Part 1 and upadacitinib in Part 2 and achieved clinical response will be re-randomized to 1 of the 2 groups in Cohort 3 (15 mg or 30 mg) and will receive 1 tablet of study drug QD.

In Substudy 3, all subjects will receive 1 tablet QD.

For subjects from Study M14-234 Substudy 1:

- Subjects who received upadacitinib 30 mg or 45 mg and achieved clinical response in Substudy 1 will be re-randomized to 1 of 3 groups in Cohort 1 (upadacitinib 15 mg, 30 mg, or placebo) and will receive 1 tablet of study drug QD as shown in Table 3.
- Subjects on upadacitinib 15 mg and achieved clinical response in Substudy 1 will be re-randomized to one of 2 groups in Cohort 1 (upadacitinib 15 mg or placebo), as shown in Table 3. Subjects on upadacitinib 7.5 mg or placebo and achieved clinical response in Substudy 1 will continue to receive the same treatment in Substudy 3 but will change from 2 tablets QD to 1 tablet QD. Placebo subjects will be in Cohort 2 and 7.5 mg subjects will be in Cohort 4.

For subjects from Study M14-234 Substudy 2 and Study M14-675:

- Subjects from Study M14-234 Substudy 2 Part 1 and Study M14-675 Part 1 who received upadacitinib 45 mg and achieved clinical response will be re-randomized to 1 of 3 groups in Cohort 1 (upadacitinib 15 mg, 30 mg or placebo) and will receive 1 tablet of study drug QD. Subjects from Study M14-234 Substudy 2 Part 2 and Study M14-675 Part 2 who received placebo in Part 1 and upadacitinib in Part 2 and achieved clinical response will be re-

randomized to 1 of the 3 groups in Cohort 1 and will receive 1 tablet of study drug QD

- Subjects from Study M14-234 Substudy 2 part 1 and Study M14-675 Part 1 who received placebo and achieved clinical response will continue to receive placebo in Cohort 2.
- Subject from Study M14-234 Substudy 2 Part 2 and Study M14-675 Part 2 who received upadacitinib in Part 1 and upadacitinib in Part 2 and achieved clinical response will be re-randomized to 1 of the 2 groups in Cohort 3 (15 mg or 30 mg) and will receive 1 tablet of study drug QD.

Table 3. Treatments Administered

Substudies	Treatment	Treatment Administered
Double-Blind Induction Doses – Phase 2b (Substudy 1):	Upadacitinib 7.5 mg Upadacitinib 15 mg Upadacitinib 30 mg Upadacitinib 45 mg Placebo	Upadacitinib 7.5 mg QD + Placebo QD Upadacitinib 15 mg QD + Placebo QD Upadacitinib 30 mg QD + Placebo QD Upadacitinib 30 mg QD + Upadacitinib 15 mg QD Matching Placebo (2 tablets) QD
Double-Blind Induction Doses – Phase 3 (Substudy 2 – Part 1):	Upadacitinib 45 mg QD Placebo	Upadacitinib 45 mg QD Matching Placebo QD
Open-Label Induction Doses – Phase 3 (Substudy 2 – Part 2):	Upadacitinib 45 mg	Upadacitinib 45 mg QD
Double-Blind Maintenance Doses – Phase 3 (Substudy 3 – Cohort 1)	Upadacitinib 15 mg Upadacitinib 30 mg Placebo	Upadacitinib 15 mg QD Upadacitinib 30 mg QD Matching Placebo QD
Double-Blind Maintenance Doses – Phase 3 (Substudy 3 – Cohort 2)	Placebo	Matching Placebo QD
Double-Blind Maintenance Doses – Phase 3 (Substudy 3 – Cohort 3)	Upadacitinib 15 mg Upadacitinib 30 mg	Upadacitinib 15 mg QD Upadacitinib 30 mg QD
Double-Blind Maintenance Doses – Phase 3 (Substudy 3 – Cohort 4)	Upadacitinib 7.5 mg	Upadacitinib 7.5 mg QD

5.5.2 Identity of Investigational Product(s)

Investigational Product	**Upadacitinib**				
Mode of Administration	Oral	Oral	Oral	Oral	Oral
Dosage Form	Film-coated tablet	Film-coated tablet	Film-coated tablet	Film-coated tablet	Film-coated tablet
Strength (mg)	7.5	15	30	45	Matching placebo
Manufacturer	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie

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, if applicable, 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

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

destroyed on site according to local procedures or regulations or returned to the destruction depot. Upon receipt of study drugs the site will acknowledge receipt within the IRT system.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally randomized using a web -based IRT.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. In Substudy 1 (Phase 2b, 8-week induction), 250 subjects who meet all the inclusion and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized in a 1:1:1:1:1 ratio to receive one of five treatment groups at Baseline (Week 0) in a double-blind manner (upadacitinib 7.5 mg QD, 15 mg QD, 30 mg QD, 45 mg QD, or placebo QD). Randomization will be stratified by previous biologic use, baseline corticosteroid use and baseline Adapted Mayo score (≤ 7 or > 7).

In Substudy 2, approximately 462 subjects will be enrolled. Eligible subjects will be randomized in a 2:1 ratio to one of the two treatment groups (double-blind upadacitinib 45 mg QD or matching placebo) for 8 weeks. The randomization will be stratified by bio-IR status (bio-IR vs non-bio-IR), corticosteroid use (yes or no), and Adapted Mayo score (≤ 7 or > 7) at Baseline. Within bio-IR, the randomization will be further stratified by number of prior biologic treatments (≤ 1 or > 1). Within non-bio-IR, the randomization will be further stratified by previous biologic use (yes or no).

After completion of the respective induction treatment period (8-weeks or Extended Treatment Period Week 16), approximately 750 subjects in Substudies 1 and 2 who received either placebo or upadacitinib 7.5, 15, 30, or 45 mg QD in Substudy 1 and those who received either placebo or upadacitinib 45 mg QD in Substudy 2 or Study M14-675 and achieved response (defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) where the Week 8 or Week 16 endoscopic subscore is determined based on local reader's assessment, will be eligible to enroll in Substudy 3 (Phase 3 52 week maintenance).

Substudy 3 will include 4 cohorts. Treatment assignment in Substudy 3 will depend on the treatment received in Substudies 1 and 2 or Study M14-675, as described in Section 5.1.2. For subjects who are eligible to be re-randomized to 1 of the 3 treatment groups in Cohort 1, randomization will be stratified by prior treatment failure (bio-IR or non-bio-IR), clinical remission status at Week 0 of Substudy 3 (yes or no), dose received in Induction Phase (only applicable to subjects from Substudy 1) and corticosteroid use at Week 0 of Substudy 3 (yes or no). For subject who are eligible to be re-randomized to 1 of the 2 treatment groups in Cohort 3, randomization will be stratified by prior treatment failure (bio-IR or non-bio-IR), clinical remission status at Week 0 of Substudy 3 (yes or no), and corticosteroid use at Week 0 (yes or no) of Substudy 3.

Subjects in Substudy 3 who meet the criteria for initial loss of response after at least 2 weeks of follow-up and have a second confirmed loss of response on a consecutive visit (unscheduled or next scheduled visit) at least 14 days later will have the option to enroll into a separate AbbVie study (Study M14-533) and receive open-label upadacitinib therapy starting from 15 mg. Loss of response is defined as a subject who presents with either:

- an SFS and RBS score each at least 1 point greater than the end-of-induction value (Week 0 of Substudy 3 or the end of induction for either Study M14-234 or Study M14-675) on 2 consecutive visits at least 14 days apart;

  OR

For subjects who had an SFS or RBS $\geq$ 2.1 at the end of induction:

- either an SFS or an RBS at least 1 point greater than the end-of-induction value (Week 0 of Substudy 3 or the end of induction for either Study M14-234 or Study M14-675) on two consecutive visits at least 14 days apart, associated with the presence of signs or symptoms of progression of UC disease as assessed by the investigator.

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 and as per Section 5.1 definitions.

IRT will provide the appropriate medication kit number(s) to dispense to each subject as per Section 5.1. Study drug will be administered at the study visits as summarized in Section 5.5. Returned study medication should not be re-dispensed to any subject.

All subjects will keep the same unique subject identification number throughout the study and program.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects in Substudies 1 and 2 will be randomly assigned to receive one of the treatment groups at Baseline by the IRT system as described in Section 5.5.3.

Substudy 1:

- Upadacitinib 7.5 mg QD
- Upadacitinib 15 mg QD
- Upadacitinib 30 mg QD
- Upadacitinib 45 mg QD
- Placebo QD

Substudy 2 (Part 1):

- Upadacitinib 45 mg QD
- Placebo QD

Substudy 2 (Part 2) – Extended Treatment Period:

- Upadacitinib 45 mg QD

Substudy 3:

For subject from Study M14-234 Substudy 1

- Subjects who received upadacitinib 30 mg or 45 mg and achieved clinical response in Substudy 1 will be re-randomized to one of 3 groups in Cohort 1 (upadacitinib 15 mg, 30 mg, or placebo) and will receive 1 tablet of study drug QD as shown in Table 3.
- Subjects on upadacitinib 15 mg and achieved clinical response in Substudy 1 will be re-randomized to one of 2 groups in Cohort 1 (upadacitinib 15 mg or placebo), as shown in Table 3.
- Subjects on upadacitinib 7.5 mg or placebo and achieved clinical response in Substudy 1 will continue to receive the same treatment in Substudy 3, but will change from 2 tablets QD to 1 tablet QD. Placebo subjects will be in Cohort 2 and 7.5 mg subjects will be in Cohort 4.

For subjects from Study M14-234 Substudy 2 and Study M14-675

- Subjects from Study M14-234 Substudy 2 part 1 and Study M14-675 part 1 who received upadacitinib 45 mg and achieved clinical response will be re-randomized to one of 3 groups in Cohort 1 (upadacitinib 15 mg, 30 mg or placebo) and will receive 1 tablet of study drug QD. Subjects from Study M14-234 Substudy 2 part 2 and Study M14-675 part 2 who received placebo in part 1 and upadacitinib in part 2 and achieved clinical response will be re-randomized to one of the 3 groups in Cohort 1 and will receive 1 tablet of study drug QD
- Subjects from Study M14-234 Substudy 2 Part 1 and Study M14-675 part 1 who received placebo and achieved clinical response will continue to receive placebo in Cohort 2.
- Subject from Study M14-234 Substudy 2 part 2 and Study M14-675 part 2 who received upadacitinib in part 1 and upadacitinib in part 2 and achieved clinical response will be re-randomized to one of the 2 groups in Cohort 3 (15 mg or 30 mg) and will receive 1 tablet of study drug QD

Subjects should take study medication as outlined in Section 5.5.

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 2 and Week 4 Visits).

Each subject's dosing schedule should be reviewed by the site at each study visit and accountability performed to ensure compliance.

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.

5.5.5 Blinding

The investigator, study site personnel, the subject and all AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment throughout the course of the study with the exception of subjects enrolled in the open label extended treatment period (Part 2) of Substudy 2. The IRT will provide access to blinded subject treatment information in the case of a medical emergency. In the event of medical situation that requires unblinding of the study drug assignment the investigator is requested to contact the AbbVie TA MD prior to breaking the blind, as long as this communication does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie agreement. In the event that the blind is broken before notification to AbbVie TA MD, it is requested that the AbbVie TA MD be notified within 24 hours of the blind being broken. Also, the date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Throughout the duration of the double-blind periods of the study, the investigator, site personnel, and subjects will remain

blinded to the subject's treatment group. AbbVie will remain blinded to the induction period data until that data is locked and analyzed as part of the planned analysis.

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 Independent Data Monitoring Committee (DMC)

Data will be unblinded for review by the independent safety Data Monitoring Committee (DMC) by an unblinded statistician not involved in the planning, execution or analysis of the study. The process for unblinding study data and ensuring its confidentiality will be described in the Data Monitoring Committee Charter for this study. The DMC will advise the sponsor as to either i) study continuation without modification, ii) study continuation with modification, iii) temporary suspension of study enrollment and/or treatment, or iv) the study should be stopped.

The external DMC composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety and if necessary, efficacy data from the ongoing study. The DMC members consist of two clinicians and one biostatistician, with one clinician being an expert in the management of subjects with UC. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

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 site 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

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

All returned study drug bottles will be inventoried by the site. Study drug bottles should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Site staff will complete study medication accountability via IRT, by using source documents and by visually inspecting the study drug bottles whenever possible. During the COVID-19 pandemic if a visit is completed virtually study drug accountability can be conducted remotely with the subject. Any kits who 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. After drug accountability has been completed, unused medication will be destroyed on site according to local procedures or regulations or returned to the destruction depot. A copy of the destruction methodology should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Upadacitinib is a potent JAK1 selective inhibitor that may provide an improved clinical benefit to risk profile in UC patients. The proposed study is a Phase 2b/3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib compared to placebo in subjects with moderately to severely active UC who have had inadequate response to, loss of response to, or intolerance to aminosalicylates, corticosteroids, immunosuppressants, or biologic therapies.

The study consists of 3 substudies. Substudy 1 is a Phase 2b dose-ranging study designed to evaluate the efficacy and safety of repeated once daily oral administration of different dose levels of upadacitinib compared with placebo as induction therapy for 8 weeks. Substudy 2 is a Phase 3 dose-confirming study designed to evaluate the efficacy and safety of repeated once daily oral administration of upadacitinib 45 mg QD, identified from Substudy 1. In Substudy 2, Part 1, upadacitinib 45 mg QD is compared with placebo as induction therapy for 8 weeks. Substudy 2, Part 2 consists of open-label upadacitinib 45 mg QD in an Extended Treatment Period for an additional 8 weeks to provide treatment for those who were treated with placebo or who did not respond to the initial 8-week upadacitinib treatment. Substudy 3 is a Phase 3 study designed to evaluate the efficacy and safety of oral administration of 2 dose levels of upadacitinib 30 mg QD and 15 mg QD compared with placebo as maintenance therapy for 44 or 52 weeks in subjects who achieved clinical response following induction with upadacitinib in Substudy 1, Substudy 2, or Study M14-675. Each substudy will have an individual statistical analysis plan.

A comparative study utilizing a placebo control design provides an unbiased assessment of the efficacy and safety profile of upadacitinib. In order to provide a potentially efficacious regimen to all participating subjects, subjects in Substudy 1 who do not achieve clinical response after completion of the 8-week induction treatment and subjects in Substudy 3 who meet the criteria for loss of response after at least 4 weeks of follow up

will have the option to enroll into a separate Phase 3 multicenter long-term extension study (Study M14-533) Cohort 1 and receive oral upadacitinib therapy.

Subjects who complete 52-week treatment in Substudy 3 will enter Cohort 2 in Study M14-533.

Data from Phase 2b and Phase 3 portions of the study will be analyzed separately (i.e., operational seamless) for the efficacy endpoints and will not be combined for statistical inference. For clinical operational efficiency, AbbVie proposes to conduct this seamless Phase 2b/3 study. The operational seamless design is proposed to allow for statistical simplicity where the Type I error controlled is well known.

Rationale of placebo use in this study

A placebo controlled study is necessary for new medication registrational purposes. Based on the guidance provided in the International Conference on Harmonization (ICH) Tripartite Guideline, Topic E10 "Choice of Control Group in Clinical Trials,"[34] a placebo-controlled trial design, using randomization and blinding has been implemented in the study in order to minimize subject and investigator bias, and support an objective assessment of all study endpoints. Current EMA guidelines on the development of new medicinal products for the treatment of Ulcerative Colitis (UC)[35] state that "unless the study is aiming at demonstrating superiority against an existing treatment, it is critical that assay sensitivity can be demonstrated, ideally by adding a placebo arm." A placebo control is the most objective comparator and a prerequisite for confirmation of clinical benefit in a Phase 3 trial.

In order to minimize the exposure to placebo during the studies, in the induction phase (Substudy 2), subjects will be randomized in a 2:1 ratio to receive upadacitinib or placebo for 8 weeks. If subjects do not respond at Week 8, an open label treatment of upadacitinib 45 mg QD will be provided for an additional 8 weeks. In the maintenance phase (Substudy 3), subjects will have 2/3 chance to be randomized to receive upadacitinib 15 mg or 30 mg QD therapy in Cohort 1, placebo responders (Cohort 2) will continue to

receive placebo, all patients in Cohort 3 and 4 will receive active drug treatment. If patients have loss of response during the maintenance phase, subjects can be enrolled into the open label cohort in long term extension Study M14-533 and receive open label upadacitinib 15 mg QD and possibly with dose escalation to 30 mg QD. Additionally, during the maintenance phase subjects can receive rescue therapy including locally acting, oral or intravenous corticosteroids, aminosalicylates, MTX or antibiotics.

It should also be noted that in this program, if the subjects are at stable and permitted dose of aminosalicylates, corticosteroids and/or methotrexate at Baseline, the treatment can be continued in the studies. Also, at any time of the study, subjects may discontinue from the study for any reason, including lack of response.

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 UC. 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 UC.

5.6.3 Suitability of Subject Population

Male and female subjects, including adults and adolescents (16 or 17 years old) when locally permissible, with moderately to severely active UC 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 those subjects with a history of inadequate response, loss of response, or intolerance to oral aminosalicylates, immunosuppressants, corticosteroids and/or biologic therapies.

5.6.4 Selection of Doses in the Study

AbbVie aims to study four doses of upadacitinib using the once-daily formulation in Substudy 1 (upadacitinib 7.5 mg QD, 15 mg QD, 30 mg QD and 45 mg QD), one

induction dose in Substudy 2 (upadacitinib 45 mg QD), and two doses in the Phase 3 maintenance Substudy 3 (upadacitinib 15 mg QD and 30 mg QD).

Dose Selection Rationale for Substudy 1

The selection of the doses was informed by the exposure-response relationship characterized in Phase 2 studies in RA, the published results for the Phase 2b study of the JAK inhibitor tofacitinib in UC,[22] and the safety margins relative to the highest doses evaluated in healthy subjects and in subjects with RA and to the preclinical toxicology no observable adverse effect level (NOAEL) exposures.

Exposure-response analysis of two Phase 2 studies in RA using the immediate-release formulations (doses from 3 mg BID to 18 mg BID and 24 mg QD) indicated that 6 mg BID dose approaches the plateau of efficacy in RA, and increasing the dose to 12 mg BID appears to result in some incremental efficacy benefit, particularly in the more refractory subjects with inadequate response or intolerance to anti-TNF biologic therapy. A bioavailability study has demonstrated that 15 mg QD and 30 mg QD regimens of the once-daily formulation provide equivalent daily AUC and comparable C_{max}, and C_{min} to 6 mg BID and 12 mg BID, respectively, of the immediate-release capsule formulation used in Phase 2 studies in RA.

It is expected that a dose higher than the efficacious dose in RA may be needed to induce clinical remission in UC. This is supported by the published data from tofacitinib Phase 2b study[22] in UC and the dose selection for tofacitinib Phase 3 study. The 45 mg dose of upadacitinib in Substudy 1 is expected to be comparable or better than the 15 mg BID dose of tofacitinib (a dose higher than the optimal dose in RA) which appeared to be already at the plateau, at least for remission. The highest dose in Substudy 1 (45 mg QD) is predicted to provide exposures comparable to (or slightly above) the NOAEL exposures from the preclinical toxicology studies as well as the highest exposures that were previously evaluated and found to be safe and well tolerated in healthy volunteers in Phase 1 and in subjects with RA in Phase 2.

The lowest dose in Substudy 1, 7.5 mg once-daily, is predicted to be sub-optimal based on the Phase 2 studies in RA, the likelihood that induction of remission in UC would require higher doses than the efficacious doses in RA, and based on the tofacitinib dose ranging study in UC, where 3 mg BID (a dose lower than the efficacious RA dose) was sub-efficacious in UC. Evaluating the 7.5 mg QD dose in Substudy 1 aims to ensure that the minimally efficacious dose is characterized.

Dose Selection Rationale for Substudy 2

The results from the Substudy 1 in subjects with UC show that all evaluated doses using the extended release (ER) tablet formulation (7.5 mg QD to 45 mg QD) were generally well tolerated and without unexpected safety concerns, consistent with the observations in Phase 2b studies in CD (Study M13-740; up to 24 mg twice daily using the immediate-release [IR] capsule formulation [exposures equivalent to 60 mg ER QD]), AD (Study M14-680; up to 30 mg ER QD), two Phase 2 studies in RA (Studies M13-537 and M13-550; up to 18 mg IR twice daily [BID] [exposures equivalent to 45 mg ER QD]) and three Phase 3 studies in RA (Studies M13-549, M13-542 and M15-555; 15 and 30 mg ER QD).

Results from the Phase 2b Induction Study M14-234 (Substudy 1) showed that upadacitinib plasma exposures associated with the 45 mg QD regimen maximize the therapeutic benefit across endpoints and across bio-IR and non-bio-IR sub-populations, at Week 8 with effect on laboratory parameters consistent with previous indications.

Preliminary exposure-response analyses for the Phase 2b Study M14-234 (Substudy 1) show that at Week 8, the percentage of subjects achieving clinical remission based on the Adapted Mayo score (primary endpoint for Phase 3), clinical response, and the endoscopic endpoints (improvement and remission) increased with increasing upadacitinib plasma exposures. With the exception of endoscopic remission, the plateau of key efficacy endpoints (clinical remission, clinical response, and endoscopic improvement) was established at Week 8 within the range of exposures evaluated in this study. Simulations using exposure-response models indicate that the upadacitinib 45 mg

QD regimen is predicted to maximize efficacy across efficacy endpoints and across bio-IR and non-bio-IR sub-populations after 8 weeks of induction treatment in subjects with UC.

The selection of the induction dose in subjects with UC is also supported by the efficacy and safety results observed in the Phase 2 study in subjects with CD (Study M13-740), wherein the two highest upadacitinib doses evaluated were 12 mg IR BID and 24 mg IR BID (equivalent of 30 mg ER QD and 60 mg ER QD). Simulations using the exposure response models indicated that a dose higher than 45 mg ER QD (60 mg ER QD) would result in only a 1% to 2% incremental efficacy in terms of clinical response and remission endpoints, and 3% to 4% higher proportions for endoscopic response and remission, while simultaneously resulting in greater decreases in NK cells and increases in CPK. Thus, the 45 mg QD dose offers the optimal benefit-risk profile and was selected as the induction dose for Phase 3 in CD.

In summary, exposures associated with upadacitinib 45 mg QD regimen are predicted to maximize efficacy across efficacy endpoints and across bio-IR and non-bio-IR sub-populations in subjects with UC while resulting in acceptable impact on laboratory parameters. Given the plateau has been established in the evaluated dose and exposure range of the Phase 2b study, a dose higher than 45 mg QD is projected to have no additional benefit for Adapted Mayo based clinical remission (primary endpoint) but can have incremental negative impact on laboratory parameters (e.g., NK cells). A dose lower than 45 mg QD is predicted to provide lower efficacy across endpoints (~2% to 10% relative to 45 mg QD).

Dose selection Rationale for Substudy 3

Substudy 3 will evaluate upadacitinib 15 mg QD and 30 mg QD for maintenance of response, which is the same dosing regimen currently being evaluated in the upadacitinib Phase 3 CD program. Using a upadacitinib lower maintenance dose than the induction dose is expected to provide a more favorable long-term safety profile compared to maintaining subjects on the dose used in induction.

Both the 15 and 30 mg ER QD doses have been proven to be efficacious in the UC induction study. Furthermore, the proposed maintenance doses of 15 mg QD and 30 mg QD using the ER formulation provide equivalent daily area under the plasma concentration-time curve (AUC) and comparable maximum plasma concentration (C_{max}) and trough (plasma) concentration measured at the end of a dosing interval (C_{trough}) to the IR formulation of upadacitinib 6 mg BID and 12 mg BID used in CD Phase 2 Study M13-740. The upadacitinib 6 mg BID and 12 mg BID doses in the Phase 2 study showed statistically significantly better endoscopic response at Week 12/16 compared to placebo. Following induction with upadacitinib 45 mg QD, doses of upadacitinib 15 mg QD and 30 mg QD are therefore expected to maintain efficacy while providing better long-term safety than higher doses.

The efficacy and safety data from the extension phase of the ongoing Phase 2 Study M13-740 also support the selection of upadacitinib 15 mg QD and 30 mg QD as the maintenance regimen. In the 36-week extension period, dose-dependent clinical and endoscopic improvements were observed at Week 52. Among subjects who received upadacitinib 6 mg BID (exposures equivalent to 15 mg ER QD) and 12 mg BID (exposures equivalent to 30 mg ER QD) and achieved clinical response at Week 16, 43% and 52% of subjects achieved modified clinical remission at Week 52, and 21% and 24% of subjects achieved endoscopic remission at Week 52, respectively. The safety profile observed during the extension phase was consistent with that reported during the induction phase, and no new safety signal was identified with the longer term upadacitinib treatment. These results support the selection of the equivalent doses of 15 and 30 mg ER QD formulation as the maintenance doses in the Phase 3 program.

The upadacitinib 15 mg QD and 30 mg QD doses are being evaluated in the Phase 3 RA clinical program. The RA program is currently evaluating > 4600 subjects, of which approximately 3700 are expected to receive upadacitinib. Periodic blinded analyses of cumulative safety data and parallel Data Monitoring Committee evaluation of unblinded safety data have not shown any unexpected adverse event.

6.0 Complaints

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

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

6.1 Medical Complaints

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding),

symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness including UC is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, [meets protocol specific criteria see Section 6.1.7 regarding toxicity management)] and/or if the investigator considers them to be adverse events.

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

6.1.1.2 Serious Adverse Events

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

Table 4. Serious Adverse Events

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

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

6.1.1.3 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 cardiovascular event [MACE]);
- Anemia;
- Neutropenia;
- Lymphopenia;
- Renal dysfunction;
- Hepatic disorders;
- Elevated creatine phosphokinase (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[26]) 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 activities of daily living (ADL) (instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
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 (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

6.1.3 Relationship to Study Drug

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

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

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

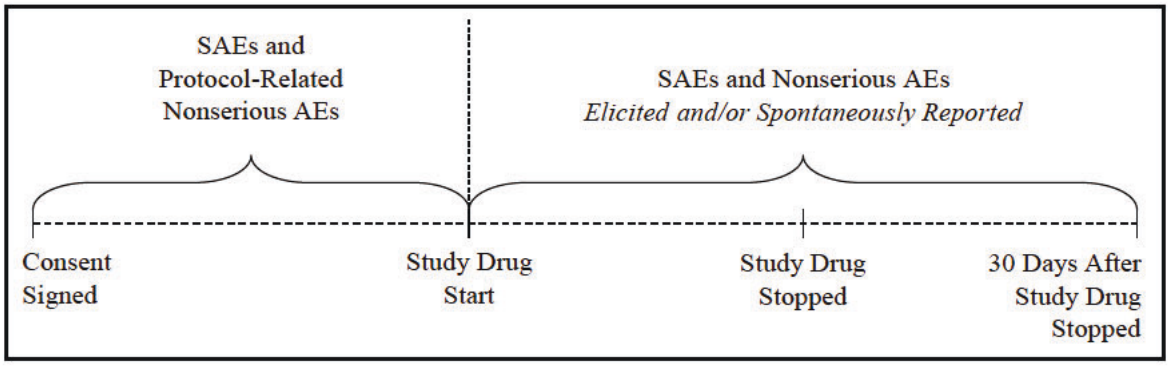
If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

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

Adverse event information will be collected as shown in Figure 5.

Figure 5. Adverse Event Collection



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, or a non-cardiac, non-CNS embolic or thrombotic event, the respective Supplemental AE eCRF should be completed.

6.1.5 Adverse Event Reporting

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

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Dept. R48S
1 North Waukegan Road
North Chicago, IL 60064

Office: (847) 938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

Primary Therapeutic Area Medical Director (TA MD):

[redacted]
200 Sydney Street
Cambridge, MA 02139
United States

Office:
Cell:
Fax:
Email: [redacted]

In emergency situations involving study subjects when the primary 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

AbbVie will be responsible for Suspected Unexpected Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

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

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

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

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

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

For subjects who discontinue study drug but continue study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central laboratory) 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 restarted once the infection has been successfully treated. These subjects will continue to be clinically monitored and will be evaluated in the safety analyses.

Subjects who develop active tuberculosis must be permanently discontinued from study drug (refer to "TB Testing/TB Prophylaxis" under Section 5.3.1.1).

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 spontaneous gastrointestinal perforation is confirmed (other

than appendicitis or mechanical injury), the subject must be permanently discontinued from study drug.

Cardiovascular Events: Subjects presenting with potential cardiovascular events including non-cardiac, non-CNS thrombotic and embolic events should be carefully monitored. These events will be reviewed and adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner.

Malignancy and Gastrointestinal (GI) Dysplasia: Subjects who develop malignancy other than nonmelanoma skin cancer (NMSC) or carcinoma in situ of the cervix, should be discontinued. Subjects who develop high grade colonic dysplasia, should be discontinued. 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.

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 non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

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 and follow any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 5, and may require a supplemental eCRF to be completed. All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 5, the repeat testing must occur as soon as possible.

Table 5. Toxicity Management Guidelines for Abnormal Lab Values

Hemoglobin	• If hemoglobin < 8.0 g/dL interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases from Baseline ≥ 3.0 g/dL 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.
Absolute neutrophil count (ANC)	• If confirmed < 1000 cells/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 that rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
Absolute lymphocyte count (ALC)	• If confirmed < 500 cells/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total white blood cell count	• If confirmed < 2000 cells/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its Baseline value.
Platelet count	• If confirmed < 50,000 cells/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. Toxicity Management Guidelines for Abnormal Lab Values (Continued)

AST or ALT	• Interrupt study drug immediately 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. • Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • Interrupt study drug immediately if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. • Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at screening who develop the following should have HBV DNA by PCR testing performed within 1 week (based on initial elevated value): o ALT > 5 × ULN OR o ALT or 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 one 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. If applicable, the alternative etiology should be documented in the eCRF. 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 that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF

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

Serum Creatinine (sCr)	• If serum creatinine is > 1.5 × the Baseline value and > ULN, repeat the test for serum creatinine (with subject in an 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 scenario, complete supplemental renal eCRF(s).
Creatine Phosphokinase	• If confirmed CPK value > 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subject may continue study drug at the investigator's discretion. • If CPK > 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. • For above CPK elevation scenarios, complete supplemental CPK eCRF.

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

Repeat testing must be performed by central laboratory.

6.1.8 Cardiovascular Adjudication Committee (CAC)

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

6.1.9 Data Monitoring Committee (DMC)

An external independent safety Data Monitoring Committee (DMC) comprised of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety and if necessary, efficacy data from the ongoing studies. The DMC members consist of two clinicians and one biostatistician, with one clinician being an expert in the

management of subjects with UC. 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 approved by AbbVie and the DMC members before a subject is initiated into the study. The DMC charter describes the composition of the DMC, the roles and responsibilities of the DMC members, frequency of data reviews and relevant safety data to be assessed, meeting occasions, and communication with AbbVie as well as relevant competent authorities.

Data for DMC review will be prepared by AbbVie (for blinded data) and an independent CRO (Axio Research for unblinded data to DMC). The DMC is responsible for monitoring safety data and alerting AbbVie to possible safety concerns related to the conduct of the study. The DMC will review safety data of the first 60 enrolled subjects in Substudy 1 of AbbVie Study M14-234 through 8 weeks of treatment to determine if there are any significant safety concerns that would warrant any study action as outlined in the DMC charter. Thereafter, the DMC will review safety data at a minimum of 6-month intervals throughout the course of the study. The DMC will determine if more frequent DMC meetings are required based on review of the accumulating safety data. In addition, ad-hoc DMC meetings will be scheduled in the event of any significant safety concerns. Based on these reviews, the DMC will make recommendations, as appropriate, regarding the conduct and management of the study. DMC recommendations will be triaged by the AbbVie Contact to the appropriate parties (AbbVie Study Management Team or Internal Review Committee).

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

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol 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 pandemic) after a subject has been

enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:	Alternate Contact:
[redacted]	[redacted]
1 North Waukegan Road North Chicago, IL 60064	1 North Waukegan Road North Chicago, IL 60064
Office: [redacted] Email:	Office: [redacted] Email:

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

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 analyses of Substudy 1 (Phase 2b induction) is to characterize the dose-response, efficacy, and safety of upadacitinib compared to placebo

in subjects with moderately to severely active UC in order to identify one induction dose of upadacitinib for further evaluation in Substudy 2 (Phase 3 induction).

The objective of the statistical analyses of Substudy 2 (Phase 3 induction) is to evaluate the efficacy and safety of the selected induction dose of upadacitinib 45 mg QD compared to placebo in subjects with moderately to severely active UC.

The objective of the statistical analyses of Substudy 3 (Phase 3 maintenance) is to evaluate the efficacy and safety of upadacitinib compared to placebo in subjects with moderately to severely active UC who had a clinical response (per Adapted Mayo score) following induction with upadacitinib.

A database lock and unblinded analysis will be conducted for the purpose of regulatory submission after the first 450 subjects in Substudy 3 Cohort 1 who were upadacitinib 45 mg QD induction responders have completed the maintenance study (i.e., completed Week 52 or prematurely discontinued prior to Week 52). This is the only and final analysis for the 52-week efficacy analyses. AbbVie study team will be unblinded to the treatment assignment, study sites and subjects will remain blinded until all subjects complete the maintenance study. If there are additional subjects in any cohort who have not completed the maintenance study at the time of database lock, they will be kept on the same blinded treatment until study completion. Once all subjects have completed the maintenance study, the data collected from these subjects will be used to update the safety analysis only.

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

8.1.1 Datasets for Analysis

8.1.1.1 Intent-to-Treat Analysis Sets

The intent-to-treat (ITT) analysis set for Substudy 1 includes all randomized subjects who received at least 1 dose of study drug from Substudy 1 (denoted as ITT1A) at the time of dose-selection analysis. The ITT analysis set that includes all ITT1A subjects, plus all the additional subjects who were randomized to upadacitinib 30 mg and 45 mg groups during the dose-selection period is denoted as ITT1B.

The ITT analysis set for Substudy 2 includes all randomized subjects who received at least one dose of double-blinded study drug from Substudy 2 (denoted as ITT2A). The ITT analysis set that includes all subjects who received the open label upadacitinib induction of 45 mg QD in the Extended Treatment Period is denoted as ITT2B.

For Substudy 3, the following ITT analysis sets are defined:

- ITT3: All subjects who received at least 1 dose of study drug in the Substudy 3.
- ITT3_A: The subset of ITT3 who were the first 450 upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1. The ITT3_A is the primary analysis population in Cohort 1 for efficacy endpoints.
- ITT3_B: The subset of ITT3 in Cohort 3 who were upadacitinib 45 mg QD 16-week induction responders.
- ITT3_C: The subset of ITT3 who were enrolled under the original protocol, Amendment 1 or 2 for 44-week maintenance treatment period.
- ITT3_D: The subset of ITT3 who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1.
- ITT3_E: The subset of ITT3 who were placebo, upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period.

Primary analysis and secondary analyses of Substudy 3 will be performed for ITT3_A, ITT3_B, ITT3_C and ITT3_E.

For the ITT analysis sets, subjects are assigned to a treatment group based on the randomization or re-randomization schedule, regardless of the treatment actually received. The efficacy analysis in each substudy will be based on the corresponding ITT analysis set.

8.1.1.2 Safety Analysis Set

The safety analysis set in each substudy consists of all subjects who received at least one dose of study medication in each portion of the study, respectively. For the safety analysis sets, subjects are assigned to a treatment group based on the treatment actually received, regardless the treatment randomized. Safety analyses of Substudy 1 to 3 will be carried out using the corresponding safety analysis set. Safety analyses of the entire study will be carried out using the union of all safety analysis sets for all treated subjects.

8.1.2 Subject Accountability

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

8.1.3 Definition of Missing Data Imputation

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

Non-Responder Imputation (NRI): In NRI analyses, subjects who prematurely discontinue the study prior to efficacy assessment at Week 8 of Substudy 1 or Substudy 2 Part 1, Week 16 of Substudy 2 Part 2, and Week 44 or Week 52 of Substudy 3 will be considered non-responders with respect to the efficacy endpoint.

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.

Depending on the magnitude of missing data due to COVID-19, additional appropriate analysis of missing data may be performed with details included in the SAP. The primary approach for handling missing data in the analysis of binary endpoints will use Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C). At each visit, subjects will be characterized as responders or non-responders based on MI imputed values if missing due to COVID-19; otherwise, subjects will be considered as non-responders for missing due to other reasons in the NRI-C approach.

For continuous endpoints, missing data will be handled using Mixed-Effect Model Repeat Measurement (MMRM).

The SFS and RBS at an assessment visit will be calculated as an average of the entries recorded into the subject's diary from the most recent consecutive 3-day period prior to each study visit. If diary entries from the 3 consecutive days prior to the visit are not available, the 3 most recent consecutive days in the last 10 days will be utilized. If data are not available for 3 consecutive days, the average of the entries from the most recent 3 non-consecutive days in the last 10 days will be utilized. If less than 3 days of diary data are available, SFS and RBS will be considered missing. Clinical endpoints of abdominal pain and bowel urgency from subject diaries will be measured at the same time period as the SFS and RBS.

Subjects in whom UC-related corticosteroids are initiated (not taken at Baseline) or who have dosages of these medications increased to greater than the dose taken at Baseline during Substudy 1 or Study 2, or UC-related rescue medications are used during Substudy 3 will be considered a failure for categorical efficacy endpoints, and for non-categorical assessments will have the last values carried forward from that time point

through the end of the substudy for Substudy 1 and will be handled by MMRM for Substudy 2 and Substudy 3.

8.1.4 Demographics and Baseline Characteristics

Baseline demographics and characteristics will be summarized for ITT analysis sets in each substudy.

8.1.4.1 Baseline Characteristics

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.

8.1.4.2 Medical Histories

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

8.1.4.3 Prior Therapy and Medications

Prior therapy and medications will include all therapies and medications administered prior to the date of the first dose of study drug. Prior therapy and medication will be summarized for the ITT analysis sets in each substudy. No statistical test will be performed.

8.1.4.4 Concomitant Medications

Concomitant drugs will be summarized for the ITT analysis sets in each substudy. Concomitant drugs will be summarized using the World Health Organization (WHO) Drug Dictionary with frequencies and percentages for each treatment group. All medications administered between the date of the first dose of study drug and the date of the last dose of study drug, inclusive, (i.e., all medications starting or ongoing during the time interval) will be included. Thus, all medications with an end date prior to the first

study drug dose will be excluded from the summary table. No statistical test will be performed.

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

8.1.5 Subject Disposition and Study Drug Exposure

8.1.5.1 Subject Disposition

The number and percentage of subjects who are enrolled, randomized and received at least one dose of study drug, and the number of subjects who prematurely discontinued and the reason for early termination will be summarized by treatment group in each substudy. Number of subjects of Substudy 1 and 2 or Study M14-675 that enter Substudy 3 will also be summarized by treatment group. Premature discontinuation of study drug will be summarized for each treatment group, as well as for all subjects combined, with frequencies and percentages overall and by reason for discontinuation for all randomized subjects who received at least one dose of study drug. Subjects may have multiple reasons for prematurely discontinuing study drug but will be counted no more than once for the total ("Any Reason").

8.1.5.2 Study Drug Exposure

Exposure to study drug will be summarized for all subjects who have received at least one dose of study drug for each substudy and over the entire study. The duration (days) of study drug treatment will be summarized with the mean, standard deviation, median and range for each treatment group. The duration of treatment is defined as the difference between the dates of the first and last doses of the treatment plus 1 day. Study drug compliance will be summarized for each treatment group. Compliance is defined as the number of tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) divided by the number of tablets a subject is supposed to take each day times the length of time that the subject was in the Treatment Phase of the

study (i.e., Final/Discontinuation Visit date during Treatment Phase – Day 1 [Baseline] Visit date +1). Subjects with missing data for the number of tablets returned will be excluded from the summary.

8.1.6 Efficacy Analysis

The primary and ranked secondary efficacy endpoints as specified in Section 5.3.3, will be tested with multiplicity adjustment to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided) within each substudy (Substudies 2 and 3). The details of the testing procedure will be specified and documented in the SAP.

8.1.6.1 Primary Efficacy Variables

The primary endpoint for Phase 2b Induction (Substudy 1) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (defined as SFS ≤ 1, RBS of 0, and endoscopic subscore ≤ 1) at Week 8.

The primary endpoint for Phase 3 induction (Substudy 2) is the proportion of subjects who achieve clinical remission per Adapted Mayo score (defined as SFS ≤ 1 and not greater than baseline, RBS of 0, and endoscopic subscore ≤ 1. Note: evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2) at Week 8.

The primary endpoint for Phase 3 maintenance (Substudy 3) is the proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 52 (for subjects who enrolled under the protocol with 44-week maintenance period, these will apply at Week 44, as applicable).

8.1.6.1.1 Analysis of Primary Endpoint

Substudy 1

The comparisons between an upadacitinib treatment group and placebo on the primary efficacy endpoint will be performed using Multiple Comparison Procedure – Modeling

(MCP-Mod) approach in the ITT1A analysis set. Subjects with missing primary endpoint data at Week 8 will be classified as "not achieved" (NRI method) for the primary endpoint.

The dose-response relationships among the four upadacitinib treatment groups and placebo group will be characterized for the primary endpoint at Week 8 using the MCP-Mod approach. The following models will be considered: log-linear, E_{max}, exponential, logistic and sigE_{max}. The MCPMod approach for trial analysis stage consists of two main steps: MCP and Mod step. The MCP step focuses on establishing evidence for a drug effect across the doses, i.e., detecting a statistically significant dose response signal for the clinical endpoint and patient population investigated in the study. This step will typically be performed using an efficient test for trend, adjusting for the fact that multiple candidate dose response models are being considered. If a statistically significant dose response signal has been established at significance level of 0.05 using two-sided test, one proceeds with determining a reference set of significant dose response models by discarding the non-significant models from the initial candidate set. The response function will be the log odds (logit) of the proportion of subjects with endoscopic/clinical remission. The fitted curve will be shown graphically with confidence intervals for each dose. Estimates of the treatment differences in the response function and associated 95% confidences for each active dose against placebo will be calculated from the model. These results will be back-transformed to give point estimates of the difference in proportions and associated 95% confidence intervals. The pairwise comparison between the treatment groups will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by previous biologic use, baseline corticosteroid use and baseline Adapted Mayo score (≤ 7 and > 7).

Primary analysis of Substudy 1 will be repeated using ITT1B population.

Substudy 2

The primary analysis will compare the subjects in upadacitinib treatment group and placebo group in the ITT2A analysis set. The difference between the treatment groups in

the primary efficacy endpoint will be assessed using the CMH test and will be stratified by baseline corticosteroid use, baseline Adapted Mayo score (≤ 7 or > 7), and bio-IR status (yes or no). The Non-responder imputation incorporating multiple imputation to handle COVID-19 (NRI-C) method will be used for primary analysis.

Primary efficacy endpoint will be summarized descriptively for the ITT2B population. Subgroup (characterized by the varying inclusion and exclusion criteria) analysis for the primary endpoint, clinical remission per Adapted Mayo score, will be conducted.

Substudy 3

The primary analysis will compare the subjects in upadacitinib treatment groups and placebo group in the ITT3_A analysis set. The difference between the treatment groups in the primary efficacy endpoint will be assessed using the CMH test and will be stratified by previous bio-IR status (yes or no), clinical remission status at Week 0 (yes or no), and cortecorsteroid use at Week 0 (yes or no). NRI-C will be used for the primary analysis.

The efficacy analyses, as applicable, will also be performed for the subset of the ITT population who only completed to Week 44 per protocol.

8.1.6.2 Secondary Efficacy Variables

All secondary efficacy variables are listed in Section 5.3.3.2.

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 Mayo score) 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-C for missing data will be used for categorical secondary endpoints.

The primary analysis and ranked secondary analysis in each substudy will be repeated in the ITT analysis sets as defined in Section 8.1.1, as appropriate.

8.1.7 Other Statistical Analyses of Efficacy

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

- Sex (male, female)
- Age (≤ median, > median)
- Race (white, non-white)
- Bio-IR status (yes, no)
- Baseline corticosteroid use (yes, no)
- Baseline Adapted Mayo score (≤ 7, > 7)
- Baseline Full Mayo score (≤ 9, > 9)
- Prior exposure to anti-TNF (yes, no)
- Prior exposure to biologic therapy (yes, no)
- Baseline weight (≤ median, > median)
- Presence of pancolitis at Baseline (yes, no)
- Disease duration at Baseline (≤ median, > median)
- Baseline hs-CRP (≤ 5 mg/L and > 5 mg/L)
- Region (US versus non-US)

For Substudy 3, the primary endpoint will also be analysed from

- Baseline aminosalicylate use (yes, no)

In addition, the following key secondary endpoints will be analyzed in bio-IR and non-bio-IR subgroup.

Induction Phase

- Endoscopic remission at Week 8
- Endoscopic improvement at Week 8
- Clinical response per adapted Mayo score at Week 8

Maintenance Phase

- Endoscopic improvement at Week 52
- Proportion of subjects who maintain clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in Study M14-234 (Substudy 1 or 2) or Study M14-675
- Propotion of subjects who achieved clinical remission at Week 52 per adapted Mayo score and were corticosteroid free for ≥ 90 days among subjects in clinical remission in the end of the induction treatment in Study M14-234 (Substudy 1 or 2) or Study M14-675.
- Proportion of subjects with endoscopic improvement at Week 52 among subjects with endoscopic improvement in Study M14-234 (Substudy 1 or 2) or Study M14-675
- Maintain Clinical response per adapted Mayo score at Week 52
- Endoscopic remission at Week 52
- Mucosal healing at Week 52

8.1.8 Safety Analysis

8.1.8.1 General Considerations

Safety analysis in Substudies 1 to 3 will be carried out using the corresponding safety analysis set. For the safety analysis of the entire study (Substudy 1, Substudy 2, and Substudy 3), all treated subjects will be included. Incidence of adverse events, including those related to study drug, changes in vital signs, physical examination results, ECGs, and clinical laboratory values will be analyzed.

Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose of the study medication and within 30 days after the last dose of the study medication. AEs will be summarized for each substudy and through the entire study. An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to early termination (see details in the SAP), AEs by Medical Dictionary for Regulatory Activities (MedDRA) 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 (ANOVA). In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

Missing safety data will not be imputed.

8.1.8.2 Analysis of Adverse Events

8.1.8.2.1 Treatment-Emergent Adverse Events

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

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

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

reporting more than one type of event within an SOC will be counted only once for that SOC.

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

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

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

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

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

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

8.1.8.2.2 Serious Adverse Events and Death

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

8.1.8.3 Analysis of Laboratory and Vital Sign Data

Changes from Baseline in continuous laboratory and vital sign parameters will be summarized by treatment group. Treatment group differences between each of the upadacitinib dosing groups and the placebo group for mean changes from Baseline will be analyzed using ANOVA.

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

8.1.9 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 estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic of renal function, etc.) will be explored using stepwise forward selection method, or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$,

corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary 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 secondary 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, 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 UC, rather than in the CSR.

Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

For Substudy 1 (Phase 2b portion of the study), a total of 250 subjects will be equally allocated to four treatment groups and the placebo group, representing a randomization ratio of 1:1:1:1:1. The sample size for this study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 8. Assuming a clinical remission rate of 12% in the placebo arm and a maximum of 30% in at least one of the upadacitinib QD treatment arms at Week 8, a sample size of 50 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest (e.g., the minimum effective dose, MED) via modeling using the MCP-Mod approach. This approach provides an average power of 68% to detect a dose effect at 5% level of significance (two-sided) with the log linear,

E_{max}, exponential, logistic and sigE_{max} models pre-specified as likely candidates to characterize the dose-response for upadacitinib for the primary endpoint of clinical remission per Adapted Mayo score.

For Substudy 2 (Part 1), a total of 462 subjects will be allocated to upadacitinib treatment group or placebo in a randomization ratio of 2:1. The sample size for this study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 8. Assuming clinical remission rate of 5% in the placebo arm and 18% of the upadacitinib QD treatment arms at Week 8, a sample size of 154 subjects in placebo and 308 subjects in upadacitinib dose will have > 95% power to detect the 13% treatment difference in the primary endpoint between an upadacitinib 45 mg QD and placebo using two-sided Fisher's exact test at a 0.05 significant level.

For Substudy 3, the sample size is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 52. Assuming clinical remission rate of 12% in the placebo arm and 40% in one of the upadacitinib QD treatment arms at Week 52, a sample size of 150 subjects in placebo and 150 subjects in each of the upadacitinib 15 mg QD and 30 mg QD treatment groups will have > 95% power to detect the 28% treatment difference in the primary endpoint between an upadacitinib dose and placebo using two-sided Fisher's exact test at a 0.025 significant level with multiplicity adjustment. Under the assumption that average response rate in upadacitinib doses at the end of Substudies 1 and 2 is 50%, a total of approximately 450 subjects will be re-randomized according to the following: subjects will be allocated to upadacitinib 15 mg QD or 30 mg QD treatment groups or placebo in a randomization ratio of 1:1:1 if they achieved a response from upadacitinib 45 mg QD in Substudy 1 and the upadacitinib 45 mg QD in Substudy 2 or Study M14-675. The assumption of an average response rate of 50% in upadacitinib doses after induction is based on the Phase 2b results.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) 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 of a state of emergency due to the COVID-19 pandemic leading 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 lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to Section 5.3.1.1 for additional details. 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.

For US subjects: at Week 8 or Week 16 (Substudy 1 or 2 or Study M14-675), subjects who will continue into Substudy 3 will sign and date a study specific IEC/IRB approved Informed Consent Form before Substudy 3 procedures are performed. The informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

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

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

Samples for exploratory research/validation studies will only be collected if the subject has voluntarily signed and dated the consent for exploratory research/validation studies, 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 written consent must be signed before the exploratory research/validation studies samples are collected and testing is performed. If the subject does not consent to the exploratory research/validation studies, it will not impact the subject's participation in the study.

For adolescent subjects, the investigator or his/her representative will explain the nature of the study and optional exploratory research samples to the subject and the subject's parent/legal guardian and answer all questions regarding this study. Adolescent subjects will be included in all discussions in order to obtain verbal or written assent. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IRB/IEC requirements, an informed assent form may also be obtained by each subject prior to any study-related procedures being performed. If a subject becomes of legal age during the course of the study, that subject will need to be re-consented. A copy of the informed consent form and the assent form will be given to the subject and the subject's parent/legal guardian and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

In the event a subject withdraws from the main study, optional exploratory research/validation studies samples will continue to be stored and analyzed unless the subject specifically withdraws consent for research involving these optional samples. If

consent is withdrawn for the optional sampling, the subject must inform their investigator, 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.

Due to the COVID-19 pandemic, 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.

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

The 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 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

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

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

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

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

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

10.3 Electronic Patient Reported Outcomes (ePRO)

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) 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 an electronic device; 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 trial. This access will be available for the duration of the trial 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 (IBDQ, SF-36, PGIC, PGIS, FACIT-F, WPAI, EQ-5D-5L, UC-SQ [UC-SQ only in select sites during Substudy 1]) will be collected electronically via an onsite device at visits specified in Appendix C and Appendix E. Stool information, abdominal pain, bowel urgency, use of anti-diarrheals and endoscopy prep will be collected electronically via a handheld device provided to the subject. 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 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference, except baseline. All PROs, except EQ-5D-5L scale, are eligible for completion by interview. If there are time constraints to the phone visit, at a minimum, the following PROs must be completed:

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

- Patient Global Impression of Change (PGIC)
- Patient Global Impression of Severity (PGIS)

Prior to conducting any phone visits to obtain PRO data 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 over the phone. The date and start and stop time of PRO data collection should be recorded along with who collected the information, their role and which questionnaires were completed.

11.0 Data Quality Assurance

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

12.0 Use of Information

All information concerning 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/validation studies 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/validation studies from this study may be used in scientific publications or presented at medical conventions. Exploratory research/validation 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 (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for 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 Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis
Protocol Date:	10 May 2021

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Hanauer SB. Update on the etiology, pathogenesis and diagnosis of ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2004;1(1):26-31.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54.e42; quiz e30.
3. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology. 2002;122(5):1500-11.
4. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohn's Colitis. 2012;6(10):965-90.
5. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451-9.
6. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. Br Med J. 1959;1(5119):387-94.
7. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501-23; quiz 524.
8. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617-25.
9. Aratari A, Papi C, Clemente V, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. Dig Liver Dis. 2008;40(10):821-6.
10. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol. 2007;5(1):103-10.

11. Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. Dig Dis. 2010;28(3):536-42.
12. Rutgeerts P, Sandborn W, Feagan B, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-76.
13. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65.
14. Feagan B, Greenberg G, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med. 2005;352(24):2499-507.
15. Sandborn W, Feagan B, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85-95; quiz e14-5.
16. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013;368(2):161-70.
17. Sandborn WJ, Chinyu S, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. New Engl J Med. 2017;376(18):1723-36.
18. Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomized, placebo-controlled trial. Lancet. 2017;389(10066):266-75.
19. Fleischmann R, Kremer J, Cush J, et al; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.
20. AbbVie. ABT-494 Investigator's Brochure Edition 6.1. 12 May 2016.
21. http://labeling.pfizer.com/Showlabeling.aspx?id=959.
22. Sandborn W, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012;367(7):616-24.

23. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

24. Sandborn WJ, et al. Presentation #OP195. United European Gastroenterology (UEG) Week. 2018

25. Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut. 2000;47(3):404-9.

26. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

27. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994;106(2):287-96.

28. Higgins PD, Schwartz M, Mapili J, et al. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. Gut. 2005;54(6):782-8.

29. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

30. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000;25(24):3130-9.

31. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ5D5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.

32. Chandran V, Bhella S, Schentag C, et al. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. Ann Rheum Dis. 2007; 66(7):936-9.

33. Reilly M. Work Productivity and Activity Impairment Questionnaire (WPAI). Reilly Associates. 2002.

34. Conference on Harmonization (ICH) Tripartite Guideline, Topic E10 "Choice of Control Group in Clinical Trials," available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf.

35. EMA draft guidelines on the development of new medicinal products for the treatment of Ulcerative Colitis (28 June 2018 CHMP/EWP/18463/2006 Rev.1).

Appendix A. Responsibilities of the Clinical Investigator

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

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

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Pharmacovigilance
		Statistics
		Statistics
		Clinical Operations
		Bioanalysis
		Clinical Pharmacology and Pharmacometrics

Appendix C. Study Activities (Substudies 1 and 2, Parts 1 and 2)

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit[d]	30-Day FU[e]
	Screening[a]	Baseline (Week 0)[b]	Week 2	Week 4	Week 6	Week 8[c]	Week 10	Week 12	Week 14	Week 16			
Informed Consent	X												
Inclusion/ Exclusion	X	X[f]											
Medical/Surgical History	X	X[f]											
Prior and Concomitant Medications[#]	X	X[f]	X	X	X	X	X	X	X	X	X	X	
Physical Exam[g,+]	X[g]	X				X				X	X	X	
Tanner Stage[g]	X (16 - 17 years old subjects only)												
Vital Signs[h,#]	X	X	X	X	X	X[h]	X	X	X	X[h]	X	X	
Schedule Endoscopy[#]	X			X				X					

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit[d]	30-Day FU[e]
	Screening[a]	Baseline (Week 0)[b]	Week 2	Week 4	Week 6	Week 8[c]	Week 10	Week 12	Week 14	Week 16			
Endoscopy[j]/ Biopsy[i,+]	X					X				X			
12-Lead ECG[k,+]	X					X				X	X		
Chest X-ray[l,+]	X												
PPD Skin Test or QuantiFERON-TB Gold Plus Test[m,+]	X												
Latent TB Risk Assessment Form[#]	X										X		
Chemistry and Hematology[n,+]	X	X	X	X	X	X	X	X	X	X	X	X	
Lipid Test[n,+]		X				X				X			
Optional biologic drug level[o]	X												
Urinalysis[p,+]	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[q,+]	X	X	X	X	X	X	X	X	X	X	X		X

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit[d]	30-Day FU[e]
	Screening[a]	Baseline (Week 0)[b]	Week 2	Week 4	Week 6	Week 8[c]	Week 10	Week 12	Week 14	Week 16			
Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential[#]	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV and HCV Screening[r,+]	X					X[s]							
HIV Ab	X												
Beta-D-Glucan (Japan Only)	X												
hs-CRP[=]	X	X	X	X	X	X	X	X	X	X	X	X	
Stool Sample (*C difficile* toxin)	X												
Provide Stool Kit[t,#]	X	X			X	X[t]			X				

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit[d]	30-Day FU[e]
	Screening[a]	Baseline (Week 0)[b]	Week 2	Week 4	Week 6	Week 8[c]	Week 10	Week 12	Week 14	Week 16			
Stool Sample (Fecal calprotectin)[t,=]		X	X			X	X			X	X		
Reminder: Stool Sample for exploratory research and validation studies (Optional – See Appendix D)[t,=]		X	X			X	X			X	X		
Upadacitinib concentration (PK assay)[u,=]			X[u]		X[u]	X[u]					X[u]		
Lymphocyte Subset[v,+]		X				X				X	X		
Samples for exploratory research and validation studies (Optional – See Appendix D)[t,=]		X	X	X		X	X	X		X	X		
Mayo Score[#]		X				X				X			

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit[d]	30-Day FU[e]
	Screening[a]	Baseline (Week 0)[b]	Week 2	Week 4	Week 6	Week 8[c]	Week 10	Week 12	Week 14	Week 16			
Partial Mayo/ Adapted Partial Mayo Score[#]		X	X	X	X	X	X	X	X	X	X	X	
Patient Questionnaires: IBDQ, SF-36, EQ-5D-5L, WPAI, FACIT-F, PGIS, UC-SQ[w,#]		X	X			X				X			
PGIC[w,#]			X			X				X			
Monitor Adverse Events[x,#]		X	X	X	X	X	X	X	X	X	X	X	X
Dispense Daily Diary[y]	X												
Daily Diary Review[y,#]		X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Administration[z,aa,#]		X		X		X[bb]		X					

Abbreviations: FU = follow-up; PD = premature discontinuation

Study activity that can be performed by phone/virtually when an onsite study visit is not possible due to COVID-19, if allowed by local regulations. This is applicable for the following Substudy 2 visits: Week 2, 4, 6, 8, 10, 12, 14, 16, PD and 30 day Follow up. All screening and Baseline visit procedures must be completed at the study site.

+ Study activity that can be performed at a local centre when an onsite study visit is not possible due to COVID-19, if allowed by local regulations. This is applicable for the following Substudy 2 visits: Week 2, 4, 6, 8, 10, 12, 14, 16, PD and 30 day Follow up. All screening and Baseline visit procedures must be completed at the study site.

= Study activity that cannot be performed by phone/virtually or at a local centre when an onsite study visit is not possible due to COVID-19. All screening and Baseline visit procedures must be completed at the study site.

a. The Screening period will be a maximum of 35 days. The Baseline Visit can be scheduled and a subject randomized at any point during this period once all eligibility criteria have been met.

b. The Baseline Visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around all study visits. Where COVID-19 affects an onsite scheduled Visit a ± 7-day window is permitted for all visits after the Baseline visit.

c. At Week 8 of Substudy 2 Part 1, if a subject is a non-responder, Week 8 will be used as the Baseline Visit for Substudy 2 Part 2.

d. Visits for dispensing new study drug in case of temperature excursion, loss or damage or visits to retest a lab are not 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.

e. Subjects will be contacted 30 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects who will continue on to Substudy 3 or Study M14-533, this will not be required until the subject completes the UC program. The home pregnancy test results will be reported at this visit and if a pregnancy is identified, the pregnancy must be reported to AbbVie as outlined in Section 6.1.6. The 30 day follow up visit should not take place sooner than 30 days after the last dose of study drug, the allowable visit window is dependent upon what phase of the study the subject was at when discontinuing study drug. During part 1 and 2 of the induction period a + 3 day window (30 to 33 days after last study drug date) is allowed.

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

g. In Substudy 2 Part 1, physical examinations performed at Screening, Baseline, Week 8/PD and Substudy 2 Part 2 at Week 16/PD Visits are full physical examinations which must include an assessment of extra-intestinal manifestations (EIMs). Physical exams at all other visits are symptom-based as necessary. Assessment of EIMs are required at every visit. For subjects 16 or 17 years of age a Tanner Stage check is to be completed during the physical examination at the screening visit, this may be completed by the investigator or by self-assessment (completed by the subject/legally authorized representative) per local requirements.

h. Height (with shoes off) will be measured at Screening only for subjects ≥ 18 years of age. For Subjects 16 or 17 years of age, height (with shoes off) will be measured at Substudy 2 screening, Week 8 and Week 16.

i. Subjects will undergo a full colonoscopy with biopsy for histologic assessment during Screening, and a full colonoscopy or flexible sigmoidoscopy, depending on the extent of disease at Screening, at Week 8. For subjects in Substudy 2 Part 2 endoscopy will be performed at Week 16, for this a flexible sigmoidoscopy is recommended at Week 16, however, the use of flexible sigmoidoscopy or colonoscopy will be based on the investigator's discretion per local practice.

j. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the investigator, must be available in order to confirm the subject's eligibility for the study. If this documentation is not available a diagnostic biopsy from the most affected observed area of the colon must be performed during the Screening endoscopy and evaluated by a qualified local pathologist and the results reviewed by the investigator. Biopsies to rule out current dysplasia and colon cancer may be taken during any study endoscopy per the investigator's discretion and evaluated by the local pathologist. During all endoscopies, up to 3 sets of biopsies will be taken (see Section 5.3.1.1 for details about biopsy sampling).

k. Subjects with normal ECG within 90 days of Screening will not require a repeat ECG, if documentation is available. The Week 8 ECG will serve as the Baseline ECG for Substudy 2 Part 2, if applicable or for Substudy 3. For subjects who enter Substudy 2 Part 2, Week 16 ECG will serve as the baseline ECG for Substudy 3.

l. Chest x-ray includes posterior-anterior and lateral views. Subjects with normal chest x-ray within 3 months of Screening will not require a repeat chest x-ray, if documentation is available. In Japan, a CT Scan of the chest may be performed in lieu of a CXR, at investigator's discretion.

m. If a subject had a negative QuantiFERON-TB Gold Plus test within 90 days of 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. PPD skin test is only to be used if the site is unable to perform the QuantiFERON-TB Gold Plus testing and is to be read 48 to 72 hours after placement.

n. It is requested to have a minimum of 8 hours fasting before any chemistry and lipid test. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

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

p. The Central Laboratory will perform the urinalysis macro and micro (if applicable). A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace. Sites will not be provided with urinalysis dipsticks.

q. A serum pregnancy test will be performed on all women of childbearing potential at Screening. In Substudy 1 and Substudy 2 Part 1urine pregnancy test will be performed at the site at Baseline and at Weeks 2, 4, 6, 8 and PD Visits and in Substudy 2 Part 2 it will be done at Weeks 10, 12, 14, and 16, and a home pregnancy test will be performed at the 30-Day Follow-up Visit for all women of child bearing potential. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. If a pregnancy is identified, the pregnancy must be reported to AbbVie as outlined in Section 6.1.6.

r. Subjects will be tested for the presence of the hepatitis B and C virus (HBV and HCV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable for any subject with positive anti-HCV AB) will be exclusionary. For subjects who are negative for HBsAg but positive for core antibody (HBcAb), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary. HBV testing is done every 12 weeks where required.

s. For Japan subjects only: Subjects with positive HBs Ab and/or positive HBc Ab results at Screening in Substudy 1 or 2 should have HBV-DNA PCR test performed at Week 8 in the induction period; 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.

t. Stool sample will be collected at each time point indicated. For the visit that endoscopy will be conducted, stool sample should be collected prior to endoscopy. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit (supplies will be provided at the time-points indicated). All stool samples should be collected before any bowel preparation for endoscopy is started and should be returned to the site within 3 days of collection. Stool sample supply kit to be provided at Week 8 visit for subjects entering into the extended treatment program.

u. Reference Section 5.3.2.1 regarding PK sample collection procedures. The Week 8 PK sample will be the Baseline PK sample for Substudy 3. PK should only be collected at the Premature discontinuation visit if the subject discontinues before the Week 8 visit, it is not relevant for subjects discontinuing during Substudy 2 Part 2.

v. Blood samples will be collected at the visits indicated and will be utilized to assess effects of upadacitinib inhibition on certain lymphocyte subsets, including T (CD4+ and CD8+) cells, B (CD19+) cells, natural killer (NK) cells, and natural killer-T (NKT) cells.

w. IBDQ = Inflammatory Bowel Disease Questionnaire; SF-36 = Short-Form 36; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Levels; WPAI = Work Productivity and Activity Impairment; FACIT F = Functional Assessment of Chronic Illness Therapy – Fatigue; PGIC = Patient Global Impression of Change. PGIC will not be collected at Baseline; UC-SQ = UC Symptoms Questionnaire. PGIS = Patient Global Impression of Severity will only be collected from subjects in Substudy 2 (Parts 1 and 2) and only at select sites.

x. Collection of Serious Adverse Events (SAEs) begins the day the subject signs the informed consent. During each study visit subjects will also be asked to report UC related Health Care Resource Utilization (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations and surgeries) and will be captured as a part of supplemental healthcare resource utilization (HCRU) form of AE collection in EDC.

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

z. Study drug will be dispensed for once daily oral intake and should be taken at the same time each day.

aa. When central or local labs cannot be collected as scheduled in the protocol due to COVID-19 pandemic, drug may be dispensed if the following criteria are confirmed. (1) There is at least 1 post-Baseline lab assessment (either Week 2 or Week 4 visit) AND (2) The investigator feels it is safe to continue based on prior labs and a phone/video call AND (3) No longer than 4 weeks have passed from the last safety lab tests.

bb. If a subject is entering Substudy 2 Part 2, investigational product will be dispensed at this visit. This is not applicable for Substudy 1 subjects or subjects in Substudy 2 Part 1 who are responders and moving into Substudy 3 at Week 8.

Appendix D. Study Activities (Substudies 1 and 2, Parts 1 and 2) Optional Samples for Exploratory Research and Validation Studies

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit	30-Day Follow-Up
	Screening	Baseline (Week 0)	Week 2	Week 4	Week 6	Week 8[a]	Week 10	Week 12	Week 14	Week 16			
Pharmacogenetic samples[b,c]		X											
Epigenetic samples[c]		X	X	X		X	X	X		X	X		
Transcriptomic and epigenetic samples[c,d]		X	X	X		X	X	X		X	X		
Plasma samples for proteomic and targeted protein investigations[c,d]		X	X	X		X	X	X		X	X		
Serum samples for proteomic and targeted protein investigations[c,d]		X	X	X		X	X	X		X	X		

Activity	Substudy 1 AND Substudy 2 Part 1 8-Week Double-Blind Induction						Substudy 2 Part 2 Extended Treatment Period				PD Visit	Unscheduled Visit	30-Day Follow-Up
	Screening	Baseline (Week 0)	Week 2	Week 4	Week 6	Week 8[a]	Week 10	Week 12	Week 14	Week 16			
Stool for biomarker analysis		X	X			X	X			X	X		
Tissue biopsy samples for transcriptomic, epigenetic, and exploratory research	X					X				X			

Abbreviations: PD = premature discontinuation

All optional samples for exploratory research and validation studies must be collected at the study site.

a. At Week 8 of Substudy 2 Part 1, if a subject is a non-responder, Week 8 will be used as the Baseline Visit for Substudy 2 Part 2.

b. The sample is preferred to be collected at Baseline but can be drawn at any time during the subject's participation.

c. Based on the value of the different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches.

d. Preferably collected while subjects are in a fasting condition.

Note: Collections to be performed only if subject provides separate written consent to collect the exploratory research/validation studies samples; if the separate consent is not signed, no samples can be collected.

Appendix E. Study Activities (Substudy 3)

Activity	Baseline of Substudy 3[a]	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/ Premature Discontinuation Visit	Unscheduled Visit[b]	30-Day Follow-Up[c]
Informed Consent	X[d]										
Prior and Concomitant Medications[#]	X	X	X	X	X	X	X	X	X	X	
Physical Exam[e,+]	X	X	X	X	X	X	X	X	X	X	
Vital Signs[f,#]	X[f]	X	X	X	X	X	X	X	X[f]	X	
Schedule Endoscopy[#]								X			
Endoscopy/Biopsy[g,+]	X								X		
12-Lead ECG[+]	X								X		
Chest X-Ray[h,+]									X		
Chemistry and Hematology[i,+]	X	X	X	X	X	X	X	X	X	X	
Lipid Test[i,+]	X				X				X		
Urinalysis[j,+]	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[k,+]	X	X	X	X	X	X	X	X	X		X

Activity	Baseline of Substudy 3[a]	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/ Premature Discontinuation Visit	Unscheduled Visit[b]	30-Day Follow-Up[c]
Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential[#]	X	X	X	X	X	X	X	X	X	X	X
hs-CRP[=]	X	X	X	X	X	X	X	X	X	X	
Latent TB Risk Assessment Form[#]				X					X		
PPD Skin Test or QuantiFERON-TB Gold Plus Test[l,+]									X[m]		
Provide Stool Kit[n,#]	X	X		X				X			
Stool Sample (Fecal calprotectin)[n,=]	X	X	X		X				X		
Upadacitinib Concentration (PK assay)[o,=]	X						X		X		
HBV DNA PCR (For Japan subjects only)[p,+]		X		X	X	X	X	X	X		

Activity	Baseline of Substudy 3[a]	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/ Premature Discontinuation Visit	Unscheduled Visit[b]	30-Day Follow-Up[c]
Reminder: Samples for exploratory research and validation studies (Optional – see Appendix F)[=]		X		X		X		X	X		
Mayo Score[#]	X								X		
Partial Mayo Score[#]	X	X	X	X	X	X	X	X	X	X	
Patient Questionnaires: IBDQ, SF-36, EQ-5D-5L, WPAI, PGIC, FACIT-F, UC-SQ, PGIS[q,#]	X								X		
Monitor Adverse Events[r,#]	X	X	X	X	X	X	X	X	X	X	X
Daily Diary Review[s,#]	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/ Administration[t,u,#]	X	X	X	X	X	X	X	X			

EQ-5D-5L = European Quality of Life 5 Dimensions 5 Levels; FACIT F = Functional Assessment of Chronic Illness Therapy – Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SF-36 = Short-Form 36; UC-SQ = Ulcerative Colitis Symptoms Questionnaire; WPAI = Work Productivity and Activity Impairment

Study activity that can be performed by phone/virtually when an onsite study visit is not possible due to COVID-19, if allowed by local regulations. This is applicable for all Substudy 3 visits.

+ Study activity that can be performed at a local centre when an onsite study visit is not possible due to COVID-19, if allowed by local regulations. This is applicable for all Substudy 3 visits.

= Study activity that cannot be performed by phone/virtually or at a local centre when an onsite study visit is not possible due to COVID-19. This is applicable for all Substudy 3 visits.

a. Subjects in Substudy 1, Substudy 2 Part 1, or Study M14-675 Part 1 who achieved response after completion of the 8-week induction treatment will be enrolled into Substudy 3. The Baseline Visit for Substudy 3 corresponds to the Week 8 Visit in Substudy 1 or Substudy 2 and serves as the reference for all subsequent visits. Subjects in Substudy 2 Part 2 or Study M14-675 Part 2 who achieved response after completion of the Extended Treatment Period (Week 16) will be enrolled into Substudy 3 and the Baseline Visit for Substudy 3 corresponds to the Week 16 Visit and serves as the reference for all subsequent visits except for PK. The PK sample collected at Week 8 of induction will be the baseline for Substudy 3. A ± 3-day window is permitted around scheduled study visits up to and included Week 12. Following completion of the Week 12 visit, a ±7-day window is permitted around scheduled study visits. Where COVID-19 affects an onsite scheduled Visit a ± 7-day window is permitted for all visits after the Baseline visit.

b. Visits for dispensing new study drug in case of temperature excursion, loss or damage are not considered an Unscheduled Visit.

c. Subjects who do not continue into the Study M14-533 will be contacted 30 days following study drug discontinuation for an assessment of any new or ongoing AEs. The home pregnancy test results will be reported at this visit and if a pregnancy is identified, the pregnancy must be reported to AbbVie as outlined in Section 6.1.6. The 30 day follow up visit should not take place sooner than 30 days after the last dose of study drug, the allowable visit window is only for 30 days or later and is dependent upon what phase of the study the subject was at when discontinuing study drug. A + 3 day window is allowed up to Week 12 (30 - 33 days after last dose of study drug) and a + 7 day window is allowed after Week 12 (30 to 37 days after last dose of study drug).

d. For US subjects only: subjects will be enrolled into Substudy 3 only after written informed consent is obtained. For subjects entering Study M14-234, Substudy 3 from Study M14-675, a new consent will be required.

e. Physical examinations performed at Baseline, Week 52 and PD Visits are full physical examinations which must include an assessment of extra-intestinal manifestations (EIMs). Physical exams at all other visits are symptom-based as necessary. Assessment of EIMs are required at every visit.

f. For Subjects 16 or 17 years of age at the time of screening, height (with shoes off) will be measured at Substudy 3 Week 0 and Week 52.

g. Subjects will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy, depending on the extent of disease at Screening in Substudy 1 or 2) with biopsy for histologic assessment at Baseline and at Week 52/PD. The local endoscopy reading will be utilized to determine the status of clinical remission for the purpose of treatment assignment in Study M14-533. During all endoscopies, up to 3 sets of biopsies will be taken (see Section 5.3.1.1 for details about biopsy sampling). For subjects who discontinue during the maintenance period (Substudy 3), an endoscopy will not be performed if the subject discontinues the study prior to the Week 28 Visit. Where COVID-19 affects the Week 52 endoscopy a –2 week and +4 week window is permitted.

h. A CXR will be performed at Week 52/PD for subjects with a positive response to TB risk questionnaire, Part 1 questions or for subjects with newly positive PPD and/or QuantiFERON-TB Gold Plus test after baseline.

i. It is requested to have a minimum of 8 hours fasting before chemistry or lipid test.

j. The Central Laboratory will perform the urinalysis macro and micro (if applicable). A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show leukocytes, nitrite, ketone, protein, blood or glucose value of greater than a trace. Sites will not be provided with urinalysis dipsticks.

k. Urine pregnancy test will be performed at Baseline and all subsequent visits for all women of child bearing potential. In home urine pregnancy test will be completed at Weeks 16, 24, 32, 40, 48 and the 30-Day Follow-up Visit. The results of the monthly at home tests will be communicated to the site. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. If a pregnancy is identified, the pregnancy must be reported to AbbVie as outlined in Section 6.1.6.

l. QuantiFERON-TB Gold Plus test is to be carried out annually from the date of the original test carried out at screening. For subjects with premature discontinuation if the Premature Discontinuation visit is ≤ 12 weeks from the prior TB test and no new known exposure of risk identified then the TB test does not need to be repeated. If the Premature Discontinuation visit is > 12 weeks from the prior TB test, the TB test will be repeated at the Premature Discontinuation visit.

m. If an annual TB test is newly positive (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB, and subsequent annual TB follow-up tests are not required.

n. Stool sample will be collected at each time point indicated. For the visit where endoscopy will be conducted, stool sample should be collected prior to endoscopy. If a sample cannot be obtained during the site visit, the site will give instructions and a stool sample supply kit (supplies will be provided at the time-points indicated). All stool samples should be collected before any bowel preparation for endoscopy is started and should be returned to the site within 3 days of collection.

o. PK samples should be collected at any time during the visit. Subject should follow the regular dosing schedule. The PK sample drawn at Week 8 of Induction will be the baseline PK sample for Substudy 3.

p. For Japan subjects only: Subjects with positive HBs Ab and/or positive HBc Ab results at Screening in Substudy 1 or 2 should have HBV-DNA PCR test performed at Weeks 4, 12, 20, 28, 36, 44, and 52/PD in Substudy 3; 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. HBV testing is done every 12 weeks where required.

q. IBDQ, SF-36, EQ-5D-5L, WPAI, FACIT F, PGIC, UC-SQ will only be collected from subjects at select sites for subjects entering from Substudy 1, for subjects entering from Substudy 2 or Study M14-675, this will be completed at all sites; PGIS = Patient Global Impression of Severity will only be collected from subjects at select sites.

r. During each study visit subjects will also be asked to report UC related Health Care Resource Utilization (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations and surgeries) and will be captured as a part of supplemental HCRU form of AE collection in EDC.

s. Subjects will continue to use the diary dispensed to them at Screening of Study M14-234 Substudy 1 or Substudy 2 or Study M14-675. All subjects should complete their subject diary on a daily basis throughout the entire study, including during hospitalizations whenever possible. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD Visit.

t. Study drug will be dispensed for once daily oral intake and should be taken at the same time each day, when possible.

u. When central or local labs cannot be collected as scheduled in the protocol during the period of COVID-19 pandemic, drug may be dispensed if the following criteria are confirmed. (1) There is at least 1 post-Week 0 lab test AND (2) The investigator feels it is safe to continue based on prior labs and a phone/video call AND (3) No longer than 12 weeks have passed from the last safety lab tests.

Appendix F. Study Activities (Substudy 3) Optional Samples for Exploratory Research and Validation Studies

Activity	Baseline of Substudy 3	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/ Premature Discontinuation Visit	Unscheduled Visit	30-Day Follow-Up
Epigenetic samples[a]		X		X		X		X	X		
Transcriptomic and epigenetic samples[a,b]		X		X		X		X	X		
Plasma samples for proteomic and targeted protein investigations[a,b]		X		X		X		X	X		
Serum samples for proteomic and targeted protein investigations[a,b]		X		X		X		X	X		
Tissue biopsy samples for transcriptomic, epigenetic, and exploratory research									X		

a. Based on the value of the different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches.

b. Preferably collected while subjects are in a fasting condition.

Note: Collections to be performed only if subject provides written consent to collect the exploratory research/validation studies samples; if the consent is not signed, no samples can be collected.

Appendix G. Patient Reported Outcomes Descriptions in Upadacitinib (ABT-494) UC Programs

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 to 70, 5 to 35, 12 to 84, and 5 to 35, respectively.[27,28]

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.[29,30]

EQ-5D-5L – European Quality of Life 5 Dimensions 5 Levels

The EQ-5D-5L is a standardized non-disease specific instrument for describing and valuing health-related quality of life. The EQ-5D-5L 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.[31]

PGIC – Patient Global Impression of Change

The PGIC is a self-administered instrument that assesses change in the overall symptoms due to UC. 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.

PGIS - Patient Global Impression of Severity

The PGIS is a self-administered instrument that assesses the severity of the overall symptoms due to ulcerative colitis. The PGIS 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."

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

The FACIT system is a collection of quality of life (QOL) questionnaires targeted to the management of cancer and other chronic illnesses. The FACIT fatigue (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 fatigue 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.[32]

WPAI – Work Productivity and Activity Impairment Questionnaire Ulcerative Colitis

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: (1) 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; (2) 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 UC on work and 10 = severe impact of UC while at work); (3) 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 (4) Activity impairment (i.e., activities other than paid work like work around house, cleaning, shopping, traveling, studying), recorded and scored in the same way as presenteeism. Higher numbers indicate greater impairment and less productivity.[33]

UC-SQ – Ulcerative Colitis Symptoms Questionnaire

The Ulcerative Colitis Symptoms Questionnaire (UC-SQ) is a UC-specific instrument composed of 17 items. UC-SQ was developed to assess UC related gastrointestinal symptoms (e.g., frequent bowel movements, abdominal pain, cramping) and non-gastrointestinal symptoms (e.g., joint pain and sleep difficulties). Each symptom item 1 - 9 can be responded on Likert-type of options such as (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. Each symptom item 10 - 17 can be responded on Likert-type of options such as (i) Never: 0 points; (ii) Rarely: 1 point; (iii) Sometimes: 2 points; (iv) Often: 3 points; (v) Always: 4 points. Overall symptom scores are calculated by combining ratings of the individual items, with higher scores indicating greater severity.

HCRU – Health Care Resource Utilization

Health Care Resource Utilization data on number of all-cause and UC-related hospitalizations and surgeries will be collected through subject Administration module SAE supplemental Page.

Appendix H. Mayo Scoring System for Assessment of Ulcerative Colitis Activity

The Mayo Scores range from 0 to 12, with higher scores indicating more severe disease. It consists of 4 subscores. Each sub-score ranges from 0 to 3. The 4 components of the Mayo Score are:

Stool **Frequency:** 0 = Normal number of stools for this subject 1 = 1 – 2 stools more than normal 2 = 3 – 4 stools more than normal 3 = 5 or more stools more than normal
Rectal **Bleeding:** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed
Findings **on Endoscopy:** 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern) 2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment**:** 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease

Note: In Study M14 -234 Substudy 2 and Substudy 3, evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

Appendix I. Screening/annual TB Risk Assessment Questionnaire Example

For Screening TB risk assessment, ask Part I and Part II questions.

For Annual TB risk assessment, only ask the Part I questions.

Part 1

1. Has an immediate family member or other close contact been newly diagnosed with or treated for active or latent tuberculosis during the last 3 months?
2. Within the past year, have you, or an immediate family member, had any of the following problems lasting for 3 weeks or longer which remained unexplained:
   - Chronic Cough
   - Production of Sputum
   - Blood-Streaked Sputum
   - Weight Loss
   - Fever
   - Fatigue/Tiredness
   - Night Sweats
   - Shortness of Breath
   - (Reference: https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm)

Part II

3. Have you ever been diagnosed or treated for active or latent tuberculosis?
4. Have you lived in or had prolonged travels to a TB endemic region?

   (reference: http://gamapserver.who.int/gho/interactive_charts/tb/cases/atlas.html)
5. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?

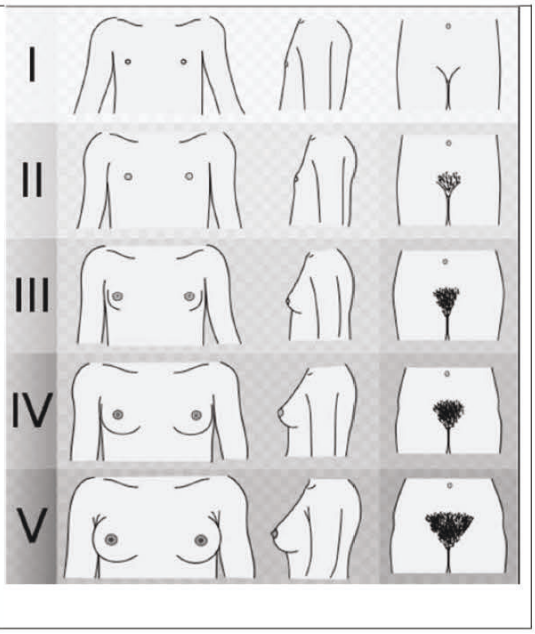
Appendix J. Tanner Staging Example

Boys

Stage	Pubic Hair	
□ 1	None	
□ 2	Scanty, long, slightly pigmented	
□ 3	Darker, starts to curl, small amount	
□ 4	Resembles adult type, less in quantity; coarse, curly	
□ 5	Adult distribution, spread to medial surface of thighs	
	Genitals	
Stage	**Penis**	**Testes**
□ 1	Preadolescent	Preadolescent
□ 2	Slight enlargement	Enlarged scrotum, pink texture altered
□ 3	Longer	Larger
□ 4	Larger, glans and breadth increase in size	Larger, scrotum dark
□ 5	Adult	Adult

Girls

Stage	Breasts
□ 1	Preadolescent
□ 2	Breast and papilla elevated as small mound, aureolar diameter increased
□ 3	Breast and areola enlarged. No contour separation
□ 4	Areola and papilla form secondary mound
□ 5	Mature, nipple projects, areola part of general breast contour
Stage	**Pubic Hair**
□ 1	None
□ 2	Sparse, lightly pigmented, straight, medial border of labia
□ 3	Darker, beginning to curl, increased amount
□ 4	Coarse, curly, abundant but amount less than in adult
□ 5	Adult feminine triangle, spread to medial surface of thighs



Appendix K. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Objective(s):
Fifth paragraph previously read:

At the time of this amendment, Substudy 2 has closed enrollment.

Has been changed to read:

At the time of this amendment, Substudy 2 has closed enrollment and all subjects have completed the induction phase.

Section 1.2 Synopsis
Subsection Objective(s):
Last paragraph
Add: new last sentence

At the time of this amendment, Substudy 3 has closed enrollment.

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Efficacy:"
Subheading "Substudy 3 Ranked Secondary Endpoints:"
Delete: item 13 and 14

13. Incidence rate of UC-related hospitalizations through Week 52
14. Incidence rate of UC-related surgeries through Week 52

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Efficacy:"
Fifth paragraph, last sentence previously read:

The Non-responder imputation (NRI) method, where subjects with missing data at scheduled assessment visits will be considered as "not achieved" for the clinical remission, will be used for primary analysis.

Has been changed to read:

Non-responder imputation incorporating multiple imputation to handle COVID-19 (NRI-C) method will be used for primary analysis.

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Efficacy:"
Eighth and ninth paragraph previously read:

Primary analysis and ranked secondary analyses of Substudy 3 will be performed for the following populations:

- The ITT analysis set includes all re-randomized subjects in Cohort 1 who received at least one dose in Substudy 3 and achieved clinical response from upadacitinib 45 mg QD in Substudies 1 and/or 2, and upadacitinib 45 mg QD in Study M14-675, denoted as ITT31. Subjects in the ITT31 analysis set who enrolled under protocol with 52-week maintenance period is defined as ITT31A. The primary analysis for Substudy 3 will be based on ITT31A population. Subjects in the ITT31 analysis set who enrolled under protocol with 44-week maintenance period is defined as ITT31B.
- The ITT analysis set includes all re-randomized subjects in Cohort 1 who received at least one dose in Substudy 3 and achieved clinical response from upadacitinib doses groups of 15 mg QD or 30 mg QD in Substudy 1, are denoted as ITT31C and ITT31D for subjects re-randomized for 44-week or 52-week maintenance, respectively.
- The ITT analysis set includes all subjects in Cohort 2 who received at least one dose in Substudy 3, denoted as ITT32.
- The ITT analysis set includes all re-randomized subjects in Cohort 3 who received at least one dose in Substudy 3, denoted as ITT33.
- The ITT analysis set includes all subjects in Cohort 4 who received at least one dose in Substudy 3, denoted as ITT34.

The comparison between treatment groups in ITT31A population for the primary efficacy endpoint will be performed using the CMH test and will be stratified by previous bio-IR status (yes or no), clinical remission status at Week 0 (yes or no), and corticosteroid use at Week 0 (yes or no). The NRI method will be used for the primary analysis.

Has been changed to read:

For Substudy 3, the following ITT analysis sets are defined:

- ITT3: All subjects who received at least 1 dose of study drug in the Substudy 3.
- ITT3_A: The subset of ITT3 who were the first 450 upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1. The ITT3_A is the primary analysis population in Cohort 1 for efficacy endpoints.
- ITT3_B: The subset of ITT3 in Cohort 3 who were upadacitinib 45 mg QD 16-week induction responders.
- ITT3_C: The subset of ITT3 who were enrolled under the original protocol, Amendment 1 or 2 for 44-week maintenance treatment period.
- ITT3_D: The subset of ITT3 who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1.
- ITT3_E: The subset of ITT3 who were placebo, upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period.

Primary analysis and secondary analyses of Substudy 3 will be performed for ITT3_A, ITT3_B, ITT3_C and ITT3_E.

The comparison between treatment groups in ITT3_A population for the primary efficacy endpoint will be performed using the CMH test and will be stratified by previous bio-IR status (yes or no), clinical remission status at Week 0 (yes or no), and corticosteroid use at Week 0 (yes or no). Non-responder imputation incorporating multiple imputation to handle COVID-19 (NRI-C) method will be used for the primary analysis.

Section 1.3 List of Abbreviations and Definition of Terms

Add:

NRI-C	Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19

Section 4.0 Study Objective
Seventh paragraph
Add: new last sentence

At the time of this amendment, Substudy 2 has closed and all subjects have completed the induction phase.

Section 4.0 Study Objective
Ninth paragraph previously read:

The secondary objective of Substudy 3 is to evaluate the efficacy of upadacitinib 30 mg QD and 15 mg QD compared to placebo in the ranked secondary endpoints at Week 52 of achieving endoscopic improvement, maintaining clinical remission, corticosteroid free remission, maintaining endoscopic improvement, endoscopic remission, maintaining clinical response, mucosal healing, no bowel urgency, no abdominal pain, histologic-endoscopic mucosal improvement, change in IBDQ total score and FACIT-F score, UC-related hospitalizations, UC-related surgeries.

Has been changed to read:

The secondary objective of Substudy 3 is to evaluate the efficacy of upadacitinib 30 mg QD and 15 mg QD compared to placebo in the ranked secondary endpoints at Week 52 of achieving endoscopic improvement, maintaining clinical remission, corticosteroid free remission, maintaining endoscopic improvement, endoscopic remission, maintaining clinical response, mucosal healing, no bowel urgency, no abdominal pain, histologic-endoscopic mucosal improvement, change in IBDQ total score and FACIT-F score.

Section 4.0 Study Objective
Last paragraph
Add: new last sentence

At the time of this amendment, Substudy 3 has closed enrollment.

Section 5.3.3.2 Secondary Variables
Last paragraph
Delete: item 13 and 14

13. Incidence rate of UC-related hospitalizations
14. Incidence rate of UC-related surgeries

Section 5.3.3.3 Additional Variables
Second paragraph previously read:

In Substudy 3, additional efficacy variables are as follows and will be evaluated at Week 52:

Has been changed to read:

In Substudy 3, additional efficacy variables are as follows and will be evaluated:

Section 5.3.3.3 Additional Variables
Second paragraph, eighth bullet previously read:

Proportion of subjects who discontinued corticosteroid use and achieved clinical remission over time in subjects taking steroids at baseline (of induction)

Has been changed to read:

Proportion of subjects who discontinued corticosteroid use and achieved clinical remission per Partial Mayo Score over time in subjects taking steroids at baseline (of induction)

Section 5.3.3.3 Additional Variables
Second paragraph, tenth and eleventh bullet previously read:

- Proportion of subjects who discontinued corticosteroid use of ≥ 90 days immediately before Week 52 and achieved a SFS ≤ 1 (and not worse than

Baseline of induction) and RBS = 1 at Weeks 40 and 48 and clinical remission at Week 52, in subjects who were taking steroids at baseline (of induction)

- Proportion of subjects who achieve clinical remission per Adapted Mayo score over time.

Has been changed to read:

- Proportion of subjects who discontinued corticosteroid use of ≥ 90 days immediately before Week 52 and achieved a SFS ≤ 1 (and not worse than Baseline of induction) and RBS = 1 at Weeks 36 and 44 and clinical remission at Week 52, in subjects who were taking steroids at baseline (of induction)

Section 5.3.3.3 Additional Variables
Second paragraph
Delete: forty second bullet

Change from Baseline in FACIT-F score over time.

Section 5.3.3.3 Additional Variables
Second paragraph
Add: new forty fifth and forty sixth bullet

- Incidence rate of UC-related hospitalizations.
- Incidence rate of UC-related surgeries.

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

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

Office:
Email: [redacted]

Has been changed to read:

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

Office:
Email: [redacted]

Section 8.1.1.1 Intent-to-Treat Analysis Sets

Third, fourth, and fifth paragraph previously read:

For Substudy 3, efficacy analyses will be based on the ITT analysis sets.

Primary analysis and ranked secondary analyses of Substudy 3 will be performed for the following populations:

- The ITT analysis set includes all re-randomized subjects in Cohort 1 who received at least 1 dose in Substudy 3 and achieved clinical response from upadacitinib 45 mg QD in Substudies 1 and/or 2, and upadacitinib 45 mg QD in Study M14-675, is denoted as ITT31. The subset of ITT31 population who are the first 450 re-randomized for 52-week maintenance is denoted as ITT31A. The subset of ITT31 population who are re-randomized for 44-week maintenance is denoted as ITT31B. The primary analysis for Substudy 3 will be based on ITT31A population.
- The ITT analysis set includes all re-randomized subjects in Cohort 1 who received at least one dose in Substudy 3 and achieved clinical response from upadacitinib ABT-494 doses groups of 15 mg QD or 30 mg QD in Substudy 1, are denoted as ITT31C and ITT31D for subjects re-randomized for 44-week or 52-week maintenance, respectively.
- The ITT analysis set includes all subjects in Cohort 2 who received at least one dose in Substudy 3, denoted as ITT32.
- The ITT analysis set includes all re-randomized subjects in Cohort 3 who received at least one dose in Substudy 3, denoted as ITT33.

The ITT analysis set includes all subjects in Cohort 4 who received at least one dose in Substudy 3, denoted as ITT34.

Has been changed to read:

For Substudy 3, the following ITT analysis sets are defined:

- ITT3: All subjects who received at least 1 dose of study drug in the Substudy 3.
- ITT3_A: The subset of ITT3 who were the first 450 upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1. The ITT3_A is the primary analysis population in Cohort 1 for efficacy endpoints.
- ITT3_B: The subset of ITT3 in Cohort 3 who were upadacitinib 45 mg QD 16-week induction responders.
- ITT3_C: The subset of ITT3 who were enrolled under the original protocol, Amendment 1 or 2 for 44-week maintenance treatment period.
- ITT3_D: The subset of ITT3 who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1.
- ITT3_E: The subset of ITT3 who were placebo, upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period.

Primary analysis and secondary analyses of Substudy 3 will be performed for ITT3_A, ITT3_B, ITT3_C and ITT3_E.

Section 8.1.3 Definition of Missing Data Imputation
Fourth paragraph previously read:

Depending on the magnitude of missing data due to COVID-19, additional appropriate analysis of missing data may be performed with details included in the SAP.

Has been changed to read:

Depending on the magnitude of missing data due to COVID-19, additional appropriate analysis of missing data may be performed with details included in the SAP. The primary approach for handling missing data in the analysis of binary endpoints will use Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C). At each visit, subjects will be characterized as responders or non-responders based on MI imputed values if missing due to COVID-19; otherwise, subjects will be considered as non-responders for missing due to other reasons in the NRI-C approach.

For continuous endpoints, missing data will be handled using Mixed-Effect Model Repeat Measurement (MMRM).

Section 8.1.3 Definition of Missing Data Imputation
Add: new last paragraph

Subjects in whom UC-related corticosteroids are initiated (not taken at Baseline) or who have dosages of these medications increased to greater than the dose taken at Baseline during Substudy 1 or Study 2, or UC-related rescue medications are used during Substudy 3 will be considered a failure for categorical efficacy endpoints, and for non-categorical assessments will have the last values carried forward from that time point through the end of the substudy for Substudy 1 and will be handled by MMRM for Substudy 2 and Substudy 3.

Section 8.1.6.1 Primary Efficacy Variables
Last paragraph previously read:

The primary endpoint for Phase 3 maintenance (Substudy 3) is the proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 44 or 52.

Has been changed to read:

The primary endpoint for Phase 3 maintenance (Substudy 3) is the proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 52 (for subjects who enrolled under the protocol with 44-week maintenance period, these will apply at Week 44, as applicable).

Section 8.1.6.1.1 Analysis of Primary Endpoint
Subsection Substudy 2
First paragraph, last sentence previously read:

The NRI method, where subjects with missing data at scheduled assessment visits will be considered as "not achieved" for the clinical remission, will be used for primary analysis.

Has been changed to read:

The Non-responder imputation incorporating multiple imputation to handle COVID-19 (NRI-C) method will be used for primary analysis.

Section 8.1.6.1.1 Analysis of Primary Endpoint
Subsection Substudy 3
First paragraph previously read:

The primary analysis will compare the subjects in upadacitinib treatment groups and placebo group in the ITT31A analysis set. The difference between the treatment groups in the primary efficacy endpoint will be assessed using the CMH test and will be stratified by previous bio-IR status (yes or no), clinical remission status at Week 0 (yes or no), and cortecorsteroid use at Week 0 (yes or no). The NRI method, where subjects with missing data at scheduled assessment visits will be considered as "not achieved" for the clinical remission, will be used for the primary analysis.

Has been changed to read:

The primary analysis will compare the subjects in upadacitinib treatment groups and placebo group in the ITT3_A analysis set. The difference between the treatment groups in the primary efficacy endpoint will be assessed using the CMH test and will be stratified by previous bio-IR status (yes or no), clinical remission status at Week 0 (yes or no), and cortecorsteroid use at Week 0 (yes or no). NRI-C will be used for the primary analysis.

Section 8.1.6.2 Secondary Efficacy Variables
Second paragraph, last sentence previously read:

NRI for missing data will be used for categorical secondary endpoints.

Has been changed to read:

NRI-C for missing data will be used for categorical secondary endpoints.

Section 8.1.7 Other Statistical Analyses of Efficacy
Add: new second paragraph and bullet list

For Substudy 3, the primary endpoint will also be analysed from

- Baseline aminosalicylate use (yes, no)

Section 8.1.8.3 Analysis of Laboratory and Vital Sign Data
First paragraph, first sentence previously read:

Changes from Baseline to minimum value, maximum value and final values in continuous laboratory and vital sign parameters will be summarized by treatment group.

Has been changed to read:

Changes from Baseline in continuous laboratory and vital sign parameters will be summarized by treatment group.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Pharmacovigilance
		Statistics
		Statistics
		Clinical Operations
		Bioanalysis
		Clinical Pharmacology and Pharmacometrics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Pharmacovigilance
		Statistics
		Statistics
		Clinical Operations
		Bioanalysis
		Clinical Pharmacology and Pharmacometrics