1.0 Title Page

Clinical Study Protocol M10-870

A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Ulcerative Colitis Who Completed the Study M11-290

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

AbbVie Investigational Product:	Adalimumab	
Date:	04 August 2021	
Development Phase:	3	
Study Design:	Phase 3, Multi-center, open-label safety and tolerability pediatric study	
EudraCT Number:	2015-001346-29	
Investigator:	Multicenter (Investigator information on file at AbbVie).	
Sponsor:	<u>European Union Countries:</u> AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany	<u>Non European Union Countries:</u> AbbVie 1 North Waukegan Road North Chicago, IL 60064
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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Amendment 0.01 (JP Only)	24 July 2014
Original	07 May 2015
Amendment 1	17 August 2015
Administrative Change 1	11 September 2015
Amendment 2	09 June 2017
Amendment 2.01 (JP Only)	27 June 2017
Amendment 3	30 July 2019
Amendment 3.01 (JP Only)	01 August 2019
Amendment 4	13 January 2021
Amendment 4.01 (JP Only)	24 March 2021

The purpose of this amendment is to add guidance about vaccines against SARS-CoV-2 and to delete language on reporting of malignancy in subjects who are 30 years old or younger:

- Section 3.3, Section 5.2.3.1, and Section 6.1.7 - removed language about collection of malignancy events in subjects who are 30 years old or younger at the time of diagnosis.

  Rationale: *Text related to the additional reporting requirements for malignancy in subjects who are 30 years old or younger (requested by the US FDA for the TNF inhibitor class in 2011) has been deleted since the postmarketing requirement was considered to be fulfilled by FDA on 21 May 2021. Of note, any malignancy events will continue to be collected as reported by the investigators.*
- Section 5.2.3.2 and Section 6.1.7 – added COVID-19 pandemic-related vaccination guidance.

  Rationale: *Language on SARS-CoV-2 vaccines and adalimumab dosing as well as documentation of SARS-CoV-2 vaccine information was added as per regulatory request.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M10-870
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 04 August 2021
Protocol Title: A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Ulcerative Colitis Who Completed the Study M11-290	
Objective: The objective of the study is to evaluate the long-term safety, tolerability, and maintenance of clinical response, of repeated administration of adalimumab in pediatric subjects with ulcerative colitis who participated in, and successfully completed, Protocol M11-290 through Week 52.	
Investigators: Multi-center	
Study Sites: Eleven sites worldwide from the main study and 3 sites from the Japan sub-study.	
Study Population: Subjects with UC who successfully completed Study M11-290.	
Number of Subjects to be Enrolled: Fifty-five subjects from the main study and 4 subjects from the Japanese sub-study	
Methodology: This study is a Phase 3, multi-center, open-label study designed to evaluate the long-term maintenance of clinical response, safety and tolerability of adalimumab in pediatric subjects with ulcerative colitis. Eleven sites worldwide (and 3 sites from Japan) that have enrolled subjects in the Study M11-290 clinical trial will participate in the Study M10-870 clinical trial. Fifty-five pediatric subjects from the main study and 4 subjects from the Japanese sub-study are expected to enroll in this study. The Week 52 visit from the Study M11-290 will serve as the Baseline Visit for subjects entering Study M10-870. Subjects will be allowed to enroll in the Study M10-870 if they have successfully completed Protocol M11-290 through Week 52 and meet all of the inclusion criteria and none of the exclusion criteria for Study M10-870. All subjects will receive open-label therapy as follows beginning at the Baseline Visit in Study M10-870: Prior to Amendment 4: • Subjects who enrolled into the study from blinded treatment in Study M11-290 were to receive open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab. • Subjects who received open label adalimumab in Study M11-290 were to maintain the same dose in Study M10-870.	

Methodology (Continued):

After Amendment 4, ongoing subjects will be switched to receive citrate free adalimumab in PFS of 20 mg, 40 mg, or 80 mg as follows:

- Subjects with a body weight < 25 kg will receive open label 20 mg eow of adalimumab
- Subjects with a body weight ≥ 25 kg - < 40 kg will receive open label 40 mg eow of adalimumab
- Subjects with a body weight ≥ 40 kg will receive open label 80 mg eow of adalimumab.

Ongoing subjects will continue to administer the remainder of dispensed vials as per the dose regimen prior to Amendment 4 until their first visit with Study Drug Dispensing after Amendment 4 when they will transition to the fixed dose regimen. Subjects who demonstrate a disease flare may have their dosage adjusted.

Prior to Amendment 4:

- Subjects who were on 0.6 mg/kg (maximum dose of 40 mg) eow of adalimumab could receive 0.6 mg/kg (maximum of 40 mg) ew of adalimumab
- Subjects who were on 0.6 mg/kg ew of adalimumab could receive 40 mg ew of adalimumab (max dose)

After Amendment 4:

- Subjects who are on 20 mg eow of adalimumab may receive 40 mg eow of adalimumab
- Subjects who are on 40 mg eow of adalimumab may receive 80 mg eow of adalimumab

Criteria for Dose Escalation (Increase) of Subjects with Disease Flare:

- Subjects with a Baseline Study M10-870 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Baseline Study M10-870 score.
- Subjects with a Baseline Study M10-870 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Baseline Study M10-870 score.
- Subjects with a Baseline Study M10-870 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Baseline Study M10-870 score.
- Subjects who present with a PMS of at least 2 points greater than their PMS at the previous visit and who are not in remission per PMS.

Prior to Amendment 4, subjects with persistently uncontrolled disease while on adalimumab 40 mg ew (max dose) were to be discontinued from the study.

After Amendment 4, subjects with persistently uncontrolled disease while on adalimumab 80 mg eow should be discontinued from the study.

Subjects who have been in remission (PMS ≤ 2 with no individual subscore > 1) for at least 8 weeks and for at least 2 consecutive visits may have their dosage de-escalated from ew to eow prior to Amendment 4 or to the next lower dose after Amendment 4. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose de-escalation.

Subjects who demonstrate disease flare after dose de-escalation have an opportunity to re escalate their dose back to adalimumab ew dosing prior to Amendment 4 or to the next higher dose after Amendment 4. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose re-escalation. One de-escalation within a period of 48 weeks and one re-escalation within a period of 48 weeks are permissible.

Methodology (Continued):

UC-related concomitant medication:

- Subjects who enroll into the study from blinded treatment in Study M11-290 will be allowed to change/initiate/discontinue their steroid dose after 4 weeks in Study M10-870.
- Subjects who enroll into the study from blinded treatment in Study M11-290 will be allowed to change/initiate/discontinue their azathioprine, 6-MP, MTX, 5-ASA doses after 8 weeks in Study M10-870.
- Subjects who enroll into the study from open label treatment in Study M11-290 will be allowed to change/initiate/discontinue their azathioprine, 6-MP, MTX, 5-ASA at any time point in Study M10-870.
- Reductions in concomitant corticosteroids, azathioprine, 6-MP, MTX, and 5-ASA will be allowed at any time in the event of moderate or severe drug-related toxicities (e.g., leukopenia, anemia, neuropathy).

The duration of the study could last up to 298 weeks (approximately 5.5 years). Subjects who complete, or who early terminate from the study will be contacted approximately 70 days after their last dose of study drug to obtain information on any ongoing and new adverse events (AEs). At study visits in addition to routine physical examination, laboratory assessments and calculation of the PMS and PUCAI, the following will be collected:

- Anthropometric evaluations at for determination of body mass index (BMI), and "z" scores for height and weight.
- IMPACT III Quality of Life questionnaire will be completed for subjects 9 years of age or older
- WPAI
- Tanner stage

This study will conclude approximately 12 weeks after one of the following criteria have been satisfied:

- Study drug received country and local (if applicable) regulatory approval for pediatric ulcerative colitis and application for local reimbursement has been submitted.
- The Sponsor determined that continuation of the study does not further promote the scientific objective of the study.

Following site notification of upcoming conclusion of the study, subjects should return to their next scheduled study visit as specified in the protocol. The termination visit should be conducted in place of their regular scheduled study visit. These subjects should be considered as having completed the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject must have successfully enrolled in and completed Protocol M11-290 through Week 52.
2. Subject of legal age, and/or parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, and/or Subject's parent, or legal guardian, as required, has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

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

Main Inclusion (Continued):

3. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subject's electronic diary.

   If a subject is of a legal age, subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections and to ensure that the time of each dose is accurately recorded in the subject's electronic diary.
4. If female, subject who is either not of childbearing potential, defined as pre-menstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of the study drug.

   Examples of approved methods of birth control include the following (see local informed consent for more detail):
   - Total abstinence from sexual intercourse;
   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD);
   - Hormonal contraceptives for 90 days prior to study drug administration;
   - A vasectomized partner.
5. Subject is judged to be in good medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding ulcerative colitis Study M11-290.

Main Exclusion:

1. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for continuing therapy in the Study M10-870.
2. Female subjects who are pregnant or currently breastfeeding or considering becoming pregnant during the study.
3. Subject with Crohn's disease (CD) or indeterminate colitis (IC).
4. History of clinically significant drug or alcohol abuse in the last 12 months.
5. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
6. History of chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, or active TB (regardless of receiving treatment), or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
7. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
8. History of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
9. Subject who is planning surgical bowel resection at any time point while enrolled in the study.
10. Known hypersensitivity to adalimumab or its excipients.
11. Current diagnosis of fulminant colitis and/or toxic megacolon.

Investigational Product:	Adalimumab
Doses:	Prior to Amendment 4: • Open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab. • Open label 0.6 mg/kg (maximum of 40 mg) ew of adalimumab. • Open label adalimumab 40 mg ew. After Amendment 4 • Open label 20 mg, 40 mg or 80 mg eow of adalimumab
Mode of Administration:	Subcutaneous injection (SC)
Reference Therapy:	NA
Dose:	NA
Mode of Administration:	NA

Duration of Treatment:

The study will include an open-label period of approximately 298 weeks. Prior to Amendment 4, all subjects were minimally on open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab beginning at the Baseline visit. After Amendment 4, all subjects will be on open label 20 mg, 40 mg or 80 mg eow of adalimumab. A 70-Day Follow-Up phone call will be completed for all subjects who either terminate early from the study or who complete the study.

Criteria for Evaluation:

Efficacy:

This study will utilize the PMS (and Mayo score if available) and PUCAI to determine efficacy of the study drug.

The following efficacy endpoints will be analyzed using summary statistics:

- The proportion of subjects who achieve clinical remission as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1) over time;
- The proportion of subjects who achieve clinical response as measured by PMS (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Baseline) over time;
- The proportion of subjects who achieve PUCAI remission (defined as < 10) over time;
- The proportion of subjects who achieve PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Baseline).

Efficacy will also be evaluated based on other measures of disease activity, including IMPACT III, WPAI, z-score for height and weight, bone age, BMI, and laboratory values as applicable. The proportion of subjects who achieve remission/response based on Mayo score and mucosal healing based on Mayo endoscopy subscore will be summarized for subjects with available Mayo score.

Pharmacokinetic and Immunogenicity:

As appropriate, population pharmacokinetic analysis and/or any additional analyses may be performed on samples for serum adalimumab concentrations and immunogenicity status collected prior to Amendment 2.

Criteria for Evaluation (Continued):

Safety:

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

Statistical Methods:

All statistical analysis results will be reported using descriptive statistics. Descriptive summary statistics will be provided for the demographic and Baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages.

Efficacy:

Summary statistics will be provided for each visit, based on observed data and non-responder imputation (NRI) for missing categorical data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subject's last non-missing, post-Baseline value (i.e., post-Week 52 Study M11-290 value) will be carried forward to the last visit. Details will be provided in the Statistical Analysis Plan (SAP).

Safety:

Treatment emergent AEs, serious adverse events (SAEs), and AEs of special interest will be summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. A summary of AEs by severity and relationship to study drug will be performed. Other safety variables such as laboratory and vital sign data will be described by descriptive statistics. In addition, shift tables and listings will be provided.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AAA	Anti-adalimumab antibody
ADA	Adalimumab
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibody
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
BLA	Biologics License Application
BUN	Blood Urea nitrogen
CD	Crohn's disease
CDC	Center for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COVID-19	Coronavirus Disease-2019
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
CXR	Chest x-ray
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
DTP	Direct-to-Patient
EC	Ethic committee
ECG	Electrocardiogram
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
Eow	Every other week
Ew	Every week
EP	European Pharmacopoeia

ESR	Erythrocyte sedimentation rate
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HCG	Human chorionic gonadotropin
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL	Interleukin
IND	Investigational New Drug
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response technology
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MTX	Methotrexate
NDC	National Drug Code
n_{nmiss}	Number of non-missing observations
PA	Posterior Anterior
PBO	Placebo
PFS	Pre-filled syringe
PK	Pharmacokinetics
POR	Proof of Receipt
PPD	Purified protein derivative
PUCAI	Pediatric Ulcerative Colitis Activity Index
QTc	QT interval corrected for heart rate
RA	Rheumatoid arthritis
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event

Sc	Subcutaneous
TB	TB Tuberculosis
Th1	Th1 Type 1 T helper
TNF	TNF Tumor necrosis factor
TPN	TPN Total parenteral nutrition
UC	Ulcerative Colitis
USP	United States Pharmacopoeia
WBC	WBC White blood cell

2.0 Table of Contents

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3.0 Introduction

3.1 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in US and EU for the treatment of RA in 2002 and 2003, respectively. Additional indications have been approved in the US and EU including Ps, PsA, AS, CD, JIA and UC. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

3.2 Ulcerative Colitis and Current Treatments and Overview

Ulcerative colitis (UC) is one of the two primary forms of idiopathic inflammatory bowel disease (IBD). It is a chronic, relapsing inflammatory disease of the rectum and/or large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The clinical course is marked by exacerbation and

remission. The general clinical features of UC are similar in adults and children; however, there are differences in the presentation and progression of the disease. While in adults, the vast majority have limited or left-sided colitis in children proximal extension of disease[1] and pancolitis involving the entire colon is more common,[2] and extra-intestinal manifestations seem to be more frequent. UC onset can occur at any age, but it is extremely rare in infants, infrequent in early childhood, and is more commonly diagnosed in late adolescence and early adulthood. Less than 1% of pediatric IBD cases occur during the first year of life, most of which are eventually diagnosed as CD and not UC.[3] Studies frequently report no,[4,5] or very few cases of UC below age 5 (11 of 211 pediatric UC cases in Great Britain and Ireland).[6] Reported incidence of UC in Europe before age 10 is also very low (per 100,000; Northern France 0.3 for ages 5 to 10,[7] Scotland 1.4 for ages 7 to 11,[8] and Northern Stockholm 1.1 for ages 5 to 9).[9] In Northern France, crude incidence of UC per 100,000 was 0.1, 0.3, 1.1, and 2.5 for age groups 0 to 5, 5 to 10, 10 to 15, and 15 to 17, respectively.[7] A prospective, population-based study in Poland in children less than age 18 reported an increase after age 10 in UC incidence (per 100,000 patient years, 0.1 age 0 to 2; 0.7 age 3 to 5; 0.9 age 6 to 10; 1.9 age 11 to 18).[10] In most pediatric studies, the median age of symptom onset was 12 years.[2]

The burden of UC on the healthcare system is profound, accounting for nearly 470,000 physician visits and more than 46,000 hospitalizations per year in the United States (US) alone.[11]

The diagnostic measures to confirm the presence of UC are essentially the same in adults and children. The diagnosis of UC is suspected on clinical grounds and supported by diagnostic testing, and elimination of infectious causes, although infection can be present in patients with UC.[2] Bloody diarrhea accompanied by tenesmus is the leading symptom in 84% to 94% of children.[1] After exclusion of infections and other causes, UC should be suspected in children if bloody diarrhea is chronic (≥ 4 weeks) or recurrent (≥ 2 episodes within 6 months), particularly when growth failure and/or pubertal delay, family history of UC/IBD, increased inflammatory markers, or anaemia are present.[2] It should be noted that growth failure is half as common in UC than in CD, perhaps because the interval

between symptoms and diagnosis is generally shorter.[2] The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published the Porto Criteria for the diagnosis of IBD (UC, CD, and IC) in children in 2005.

Disease of moderate or severe activity may often be associated with anorexia, nausea, weight loss, and fever, as well as symptoms associated with anemia and hypoalbuminemia. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extraintestinal complications include arthritis (sacroiliitis and ankylosing spondylitis), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.[12]

The pharmacological treatment of UC in childhood is largely the same as in adulthood. Conventional pharmaceutical therapies do not completely abate the inflammatory process and have significant side effects. Conventional therapies for the induction of remission have included anti-inflammatory agents (5-aminosalicylic acid [5-ASA] derivatives and corticosteroids) and the immunomodulatory agent cyclosporine. 5-ASA derivatives as well as immunomodulatory agents (azathioprine or 6-mercaptopurine [6-MP]) have been used for the maintenance of remission.[13] Corticosteroids are not effective for the maintenance of remission. In addition to the induction and maintenance of clinical remission, absence of adverse effects on linear growth and maturation is demanded from therapy of pediatric UC. Similar to adults, corticosteroid dependence is frequent, but long-term corticosteroids are absolutely contraindicated because they do not maintain remission and have a negative effect on linear growth and bone mineralization.[2] Infliximab (a chimeric monoclonal anti-tumor necrosis factor [TNF]-α antibody) was approved in Europe for the treatment of pediatric patients with severe UC and in the US for the treatment of pediatric patients with moderate to severe UC based on the results of a recent study.[14]

The safety and efficacy of adalimumab for the induction and maintenance of clinical remission in adult subjects with moderately to severely active UC has been studied in two completed clinical trials (Study M06-826 and Study M06-827) and an ongoing open-label study (Study M10-223).[15-18] In addition, adalimumab has shown clinically relevant improvements in IBDQ scores compared to placebo for up to 52 weeks in these subjects.[19]

3.3 Safety Information

Adalimumab therapy has a well established and well described safety profile in adults based on extensive postmarketing experience and continued clinical trial-subject exposure since the first approved indication in 2002 for rheumatoid arthritis. In general, the safety profile observed in pediatric studies is consistent with that in the adult population. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency.

3.3.1 Differences Statement

Pediatric subjects with moderate-to-severe UC between the ages of 4 and 17 who participated in, and successfully completed, Protocol M11-290 through Week 52 will be considered for participation in the study.

3.4 Benefits and Risks

Extensive clinical and postmarketing experience exists with adalimumab in a wide range of disease states including the IBD indications Crohn's disease and UC. The safety profile of adalimumab in those indications is well established with more than 50,000 patient-years of adalimumab clinical trial experience. The clinical studies in adult UC have not altered this safety profile and demonstrated a positive benefit/risk balance.

Conditions which may present a risk specifically for subjects with UC are exclusion criteria in this study (e.g., evidence of colonic dysplasia or active infections).

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving adalimumab may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for ulcerative colitis, no change to the benefit/risk balance for subjects in this study is expected. Current published information suggests that the baseline use of biologics is not associated with worse Covid-19 outcomes.[20]

4.0 Study Objective

The objective of the study is to evaluate the long-term safety, tolerability, and maintenance of clinical response, of repeated administration of adalimumab in pediatric subjects with ulcerative colitis who participated in, and successfully completed, Protocol M11-290 through Week 52.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study was designed to enroll approximately 85 subjects from the main study and approximately 8 subjects from the Japan sub-study to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Fifty-five pediatric subjects with moderate-to-severe ulcerative colitis who participated in, and successfully completed, Protocol M11-290 through Week 52 will be enrolled at 11 sites worldwide (Section 5.3.1.1).

There also will be 4 Japanese subjects in a Japan sub-study to be enrolled at 3 Japan sites. The Japan sub-study will be conducted utilizing the same design as outlined in the main study with the exceptions that are outlined in a separate Japan specific protocol.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study and will receive open-label study drug. At the Baseline visit, the following procedures will be completed as part of Week 52 of the M11-290 protocol: concomitant medication updates, physical exam, vital signs, Chemistry/hematology, hs-CRP, urinalysis, pregnancy test, TB testing, Mayo Score, PMS, PUCAI, IMPACT III Questionnaire, WPAI UC-Caregiver, Tanner Stage, Anthropometric Evaluations, endoscopy and monitoring of adverse events as well as subject diary dispensing/reviewing. Medical History will be updated from the medical history recorded during the subject's previous study.

All subjects will receive open-label therapy as follows beginning at the Baseline Visit in Study M10-870:

Prior to Amendment 4:

- Subjects who enrolled into the study from blinded treatment in Study M11-290 were to receive open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab.
- Subjects who received open label 0.6 mg/kg (maximum of 40 mg) ew of adalimumab in Study M11-290 were to maintain the same dose in Study M10-870.

After Amendment 4, ongoing subjects will be switched to receive a fixed-dose regimen, by weight cut-off, incorporating citrate free adalimumab in PFS (20 mg, 40 mg, or 80 mg) as follows:

- Subjects with a body weight < 25 kg will receive open label 20 mg eow of adalimumab

- Subjects with a body weight ≥ 25 kg - < 40 kg will receive open label 40 mg eow of adalimumab
- Subjects with a body weight ≥ 40 kg will received open label 80 mg eow of adalimumab.

Ongoing subjects will continue to administer the remainder of dispensed vials as per the dose regimen prior to Amendment 4 until their first visit with Study Drug Dispensing after Amendment 4 when they will transition to the fixed dose regimen.

The duration of the study could be up to 298 weeks, which includes a 288-week open-label maintenance period and a 70-day follow-up. There is a ± 3 day window for all study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

Efficacy and safety measurements will be performed throughout the study (see Table of Activities, Section 5.3.1). Clinical evaluation will be performed at Baseline, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264 and 288/Premature Discontinuation and unscheduled Visits. Subjects may undergo an optional endoscopy during Weeks 48, 96, 192, and 288/Premature Discontinuation Visit to assess disease activity and for surveillance per the investigator's discretion.

Treatment of Subjects with a Disease Flare

Criteria for Disease Flare are as follows:

- Subjects with a Baseline Study M10-870 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Baseline Study M10-870 score.
- Subjects with a Baseline Study M10-870 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Baseline Study M10-870 score.
- Subjects with a Baseline Study M10-870 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Baseline Study M10-870 score.
- Subjects who present with a PMS of at least 2 points greater than their PMS at the previous visit and who are not in remission per PMS.

Prior to Amendment 4:

- Subjects with a disease flare who were on 0.6 mg/kg (maximum dose of 40 mg, weight based) eow of adalimumab could receive 0.6 mg/kg (maximum of 40 mg, weight based) ew of adalimumab.
- Subjects with a disease flare who were on 0.6 mg/kg ew of adalimumab could receive 40 mg ew (maximum dose of 40 mg).

Subjects with persistently uncontrolled disease while on adalimumab 40 mg ew (max dose) were to be discontinued from the study.

After Amendment 4:

- Subjects who are on 20 mg eow of adalimumab may receive 40 mg eow of adalimumab.
- Subjects who are on 40 mg eow of adalimumab may receive 80 mg eow of adalimumab.

Subjects with persistently uncontrolled disease while on adalimumab 80 mg eow should be discontinued from the study.

The Investigator should consider dose escalation in lieu of initiating any rectal therapy such as therapeutic enemas or suppositories during the study. The AbbVie study designated physician identified in Section 6.1.7 should be contacted if there are any questions regarding rectal therapy.

Dose De-Escalation and Re-Escalation

Subjects who have been in remission (PMS $\leq$ 2 with no individual subscore > 1) for at least 8 weeks and for at least 2 consecutive visits may have their dosage decreased from ew to eow prior to Amendment 4 or to the next lower dose after Amendment 4. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose de-escalation.

Subjects who demonstrate disease flare after dose de-escalation have the opportunity to re-escalate their dose back to adalimumab ew dosing prior to Amendment 4 or to the next higher dose after Amendment 4. The investigator should receive prior approval from the medical monitor before taking any action with regard to dose re-escalation. One de-escalation within a period of 48 weeks and one re-escalation within a period of 48 weeks are permissible.

No study drug will be administered or injected at the final visit.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have a Termination Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing AEs.

An Example of 70-Day Follow-Up Call – Form is described in Appendix G.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

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

1. Subject must have successfully enrolled in and completed Protocol M11-290 through Week 52.
2. Subject of legal age, and/or parent or legal guardian, as required, has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form, after the nature of the study has been explained and the subject of legal age, and/or Subject's parent, or legal guardian, as required, has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed. Subjects will be included in all discussions, and if required, their signature on an assent form will be obtained.

3. Parent or legal guardian of subject who is not of legal age, as required, must be willing to actively supervise storage and administration of study drug and to ensure that the time of each dose is accurately recorded in the subject's electronic diary.

   If a subject is of a legal age, subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections and to ensure that the time of each dose is accurately recorded in the subject's electronic diary.

4. If female, subject who is either not of childbearing potential, defined as pre-menstrual, or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of the study drug.

   Examples of approved methods of birth control include the following (see local informed consent for more detail):

   - Total abstinence from sexual intercourse;
   - Condoms, sponge, foam, jellies, diaphragm or intrauterine device (IUD);
   - Hormonal contraceptives for 90 days prior to study drug administration;
   - A vasectomized partner.

5. Subject is judged to be in good medical condition, as determined by the Principal Investigator based upon results of clinical and laboratory evaluations done throughout the preceding ulcerative colitis Study M11-290.

5.2.2 Exclusion Criteria

1. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for continuing therapy in the Study M10-870.
2. Female subjects who are pregnant or currently breastfeeding or considering becoming pregnant during the study.
3. Subject with Crohn's disease (CD) or indeterminate colitis (IC).

4. History of clinically significant drug or alcohol abuse in the last 12 months.
5. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
6. History of chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, or active TB (regardless of receiving treatment), or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
7. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
8. History of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
9. Subject who is planning surgical bowel resection at any time point while enrolled in the study.
10. Known hypersensitivity to adalimumab or its excipients.
11. Current diagnosis of fulminant colitis and/or toxic megacolon.

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 receives during the study, must be recorded in source documents and on the appropriate page of the electronic case report form (eCRF), along with the reason for use, dates of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie study designated physician identified in Section 6.1.7 should be contacted if there are any questions regarding concomitant or prior therapy.

Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

5.2.3.2 Concomitant Therapy

UC-related concomitant medication:

- Subjects who enroll into the study from blinded treatment in Study M11-290 will be allowed to change/initiate/discontinue their steroid dose after 4 weeks in Study M10-870.
- Subjects who enroll into the study from blinded treatment in Study M11-290 will be allowed to change/initiate/discontinue their azathioprine, 6-MP, MTX, 5-ASA doses after 8 weeks in Study M10-870.
- Subjects who enroll into the study from open label treatment in Study M11-290 will be allowed to change/initiate/discontinue their steroid, azathioprine, 6-MP, MTX, 5-ASA doses at any time point in Study M10-870.
- Reductions in concomitant corticosteroids, azathioprine, 6-MP, MTX, and 5-ASA will be allowed at any time in the event of moderate or severe drug-related toxicities (e.g., leukopenia, anemia, neuropathy).

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

Subsequent changes in all concomitant medications will be assessed at each study visit from Baseline (Week 0) through Week 288/Premature Discontinuation Visits. All subjects will be given a Subject Medication Log to help track any change in therapy. These changes will be documented in the source documents and captured on the appropriate eCRF page.

All non-UC medications (prescription and over-the-counter) used will be recorded and must include all doses and date ranges of administration. Vaccines administered to the subject will be listed as a concomitant medication. Any antibiotic used will be recorded and must include all doses and date ranges of administration.

The AbbVie Study Designated Physician identified in Section 6.1.7 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

COVID-19 Pandemic -Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during the study as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of adalimumab on SARS-CoV-2 vaccination is unknown. Therefore, adalimumab should be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to Section 6.1.7 for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- Biologic therapy with a potential therapeutic impact on ulcerative colitis including but not limited to the following:
  - Anakinra (Kineret®);
  - Abatacept (Orencia®);
  - Natalizumab (Tysabri®);
  - Efalizumab (Raptiva®);
  - Infliximab (Remicade®);
  - Etanercept (Enbrel®);
  - Rituximab (Rituxan®);
  - Tocilizumab (Actemra®);
  - Golimumab (Simponi®);
  - Certolizumab (Cimzia®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Vedolizumab (Entyvio®).
- The use of Tofacitinib (Xeljanz®) is prohibited during the study.
- Live vaccines (during the study and for 70 days after the last dose of study drug).
- The use of systemic cyclosporine, tacrolimus, or mycophenolate mofetil is prohibited during the study.
- Intravenous corticosteroid use is prohibited during the study.
- The use of investigational drugs of chemical or biologic nature are prohibited during the study.

The AbbVie study designated physician identified in Section 6.1.7 should be contacted if there are any questions regarding prohibited therapy.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in Table 1. There is a ± 3-day window for all study visits.

Allowed protocol modifications due to states of emergency or pandemic situations are detailed in this section.

Table 1. Study Activities

Activity	Baseline (Week 0)[a]	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132 Call[s]
Informed Consent	X													
Inclusion/Exclusion	X													
Medical/Surgical History	X[d]													
Tobacco and Alcohol Use	X[d]													
Previous and Concomitant Medication	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[e]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Endoscopy (optional)[f]	X[d]						X				X			
Physical Examination[g]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
TB testing[h]	X[d]						X				X			
Chemistry and Hematology[i]	X[d]	X		X	X	X	X	X	X	X	X	X	X	
Urinalysis[j]	X[d]	X			X		X		X		X		X	
Pregnancy Tests[k,l]	X[d]	X[l]	X[l]	X[l]	X[l]	X[l]	X[k]	X[l]	X[l]	X[l]	X[k]	X[l]	X[l]	
hs-CRP[i]	X[d]				X		X		X		X		X	
PUCAI	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Partial Mayo Score	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Mayo Score[f]	X[d]						X				X			
IMPACT III Questionnaire[m]	X[d]				X		X		X		X		X	
Work Productivity and Impairment Questionnaire (WPAI): UC – Caregiver[n]	X[d]				X		X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Baseline (Week 0)[a]	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132 Call[s]
Tanner Stage	X[d]						X				X			
Anthropometric Evaluations	X[d]				X		X		X		X			
X-ray for Bone Age[o]	X[d]						X				X			
Monitor Adverse Events[p]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Diary Dispensing/Reviewing[q]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Dispensing/Administration[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Activities (Continued)

Activity	Week 144	Week 156 Call[s]	Week 168	Week 180 Call[s]	Week 192	Week 204 Call[s]	Week 216	Week 228 Call[s]	Week 240	Week 252 Call[s]	Week 264	Week 276 Call[s]	Week 288/ Premature Discontinuation	Unscheduled Visit[b]	70-Day Follow-Up Call[c]
Informed Consent															
Inclusion/Exclusion															
Medical/Surgical History															
Tobacco and Alcohol Use															
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[e]	X		X		X		X		X		X		X	X	
Endoscopy (optional)[f]					X								X		
Physical Examination[g]	X		X		X		X		X		X		X	X	
TB testing[h]	X				X				X				X		
Chemistry and Hematology[i]	X		X		X		X		X		X		X	X	
Urinalysis[j]	X		X		X		X		X		X		X	X	
Pregnancy Tests[k,l]	X[k]		X[l]		X[k]		X[l]		X[k]		X[l]		X[k]		
hs-CRP[i]	X		X		X		X		X		X		X	X	
PUCAI	X		X		X		X		X		X		X	X	

Table 1. Study Activities (Continued)

Activity	Week 144	Week 156 Call[s]	Week 168	Week 180 Call[s]	Week 192	Week 204 Call[s]	Week 216	Week 228 Call[s]	Week 240	Week 252 Call[s]	Week 264	Week 276 Call[s]	Week 288/ Premature Discontinuation	Unscheduled Visit[b]	70-Day Follow-Up Call[c]
Partial Mayo Score	X		X		X		X		X		X		X	X	
Mayo Score[f]					X								X		
IMPACT III Questionnaire[m]	X		X		X		X		X		X		X		
Work Productivity and Impairment Questionnaire (WPAI): UC – Caregiver[n]	X		X		X		X		X		X		X		
Tanner Stage	X				X				X				X		
Anthropometric Evaluations	X				X				X				X		
X-ray for Bone Age[o]	X				X				X				X		
Monitor Adverse Events[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Diary Dispensing/ Reviewing[q]	X		X		X		X		X		X		X	X	
Study Drug Dispensing/ Administration[r]	X		X		X		X		X		X			X	

Table 1. Study Activities (Continued)

a. The Baseline visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits.

b. Procedures performed as needed.

c. Site personnel will contact all subjects approximately 70 days following study drug discontinuation to determine the occurrence of AEs or SAEs.

d. At the Baseline visit, the following procedures for Study M10-870 will be completed as part of Week 52 of the Study M11-290 protocol: tobacco & alcohol use; concomitant medication changes, physical exam, vital signs, Chemistry/hematology, hs-CRP; PUCAI; urinalysis, pregnancy test; TB testing, Partial Mayo Score; Mayo Score, IMPACT III Questionnaire, WPAI UC-Caregiver, Tanner Stage, Anthropometric Evaluations, X-ray for Bone age; endoscopy, adverse events and subject diary dispensing/reviewing. Medical History will be updated from the medical history recorded during the subject's previous study.

e. Vital sign determinations of weight, sitting blood pressure, pulse rate, respiratory rate, body temperature will be obtained at each visit.

f. The endoscopy is optional at Weeks 48, 96, 192 and 288/Premature Discontinuation. In this case, endoscopies may be either flexible sigmoidoscopy or colonoscopy. Biopsies to rule out malignancy, dysplasia, and infection may be taken at the investigator's discretion. Mayo score is dependent on availability of endoscopy.

g. Physical examinations performed at Weeks 48, 96, 144, 192, 240, and 288/Premature Discontinuation Visits are full physical examinations and those performed at all other visits are symptom based.

h. For subjects with a negative TB test, a TB test will be required at Weeks 48, 96, 144, 192, 240 and 288. If the annual TB screen is positive, a CXR may be required for evaluation of active TB. Annual TB screening will not be required for subjects who have been treated for latent or active TB or have had a positive TB test at any time (prior to the study, or testing performed at any time point during Study M11-290). For such subjects, annual evaluation by a physician for clinical signs/symptoms of active TB (including a directed TB history and physical exam including lungs, lymph nodes and skin) or newly identified TB risk factors will be required at Weeks 48, 96, 144, 192, 240 and 288.

i. Blood draws should be performed after completion of all clinical assessments and questionnaires.

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

k. All females of childbearing potential will have a serum pregnancy test at Weeks 48, 96, 144, 192, 240 and 288/Premature Discontinuation Visit.

l. At Week 4 visit and all subsequently scheduled study visits, all females of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study.

Table 1. Study Activities (Continued)

m. IMPACT III Quality of Life questionnaire at Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288/Premature Discontinuation Visit will be completed for subjects 9 years of age or older at the baseline study visit.

n. WPAI will be completed by subject's parent or legal guardian at Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288/Premature Discontinuation Visit. The questionnaire will not be completed if the subject's parent or legal guardian is not taking care of the subject anymore.

o. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age can be omitted. Assessment of bone age is not required for subjects at the Premature Discontinuation Visit.

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

q. Subjects will be dispensed a subject diary at Baseline and will be trained on how to complete the diary by site staff during the Baseline visit. All subjects should complete their subject diary on a daily basis throughout the entire study, including if and when hospitalized whenever possible. The diary will be reviewed by site personnel with the subject at each visit and collected at the Week 288/Premature Discontinuation Visit.

r. Study drug may be dispensed at the Unscheduled Visit if there is a change in the dosing schedule (i.e., subject meets criteria of disease flare) or if damaged drug needs replacement.

s. Phone calls will be made to collect information on concomitant medications and AE/SAE's.

5.3.1.1 Study Procedures

The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of adverse event (AE) information (discussed in Section 6.1.2). All study data will be recorded in source documents and on the appropriate eCRFs.

Study visits may be impacted due to states of emergency or pandemic situations. This may include changes such as phone or virtual visits, among others. 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.

States of Emergency or Pandemic -Related Acceptable Protocol Modifications

During states of emergency or pandemic situations, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

Study visits and/or activities may be performed by phone/virtually. These are indicated below;

- Assess safety (AEs/concomitant medications/contraception, investigation product compliance/dosing (including last date and dose of study drug));
- Investigator assessments (ex. Physician Global Assessment in Partial Mayo Score and Mayo Score) can be completed by using the applicable subscores and by patient interview.
- IMPACT III and WPAI questionnaires will be completed over the telephone/virtual meeting;
- Please ensure that the subject completes ePRO diary entries and confirm with the subject that diary entries are being completed.
- The subject must be weighed at home and provide it to the study site so that the dose to be administered can be determined. If there is a deviation in weight >10% from the previous body weight, site and parent/subject should determine if this is due to calibration of scales between site and home scale.

- During a virtual visit, the following activities do not need to be performed: vital signs (except weight), physical exam, Tanner Stage, height (for anthropometric evaluation), and bone age.
- Lab samples (including pregnancy test for females of childbearing potential) may be performed by a local clinic/hospital/laboratory. All procedures performed at local facilities must be performed by appropriately qualified personnel. If lab samples cannot be collected, the study drug cannot be dispensed to the subject. Any local labs should be collected and reported in alignment with the protocol requirements and reviewed by the investigator as soon as possible.
- Study Visits and/or activities should be performed as scheduled whenever possible.
- If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity.

Inclusion/Exclusion Criteria

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

Informed Consent

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific informed consent will be reviewed, signed and dated by the parent or their guardian before any study procedures are undertaken, or before any concomitant medications are withheld from the subject in order to participate in this study. Pediatric subjects will be included in all discussions. If a subject becomes of legal age in the state of residence during the course of the study, an informed consent will need to be obtained at that time. Additionally, in complying with each institution's IRB requirements, an informed assent may also be obtained from the subject.

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

Before informed consent may be obtained, the investigator or designee will explain the nature and purpose of the study and its procedures to the subject. Ample time and opportunity for the subject or the parent or their guardian, or the subject's legally acceptable representative to ask any questions about the study will be provided, so that an informed consent can be made as to whether or not to participate in the study. All questions about the study will be answered to the satisfaction of the subject.

After the informed consent is signed and dated by the parent or guardian, the person who discussed the informed consent will also sign and date the document and provide a copy of the informed consent to the subject. The original informed consent will be placed in the subject's medical record with documentation that the informed consent was signed prior to the performance of any study procedures and that the subject was given a signed and dated copy.

Due to states of emergency or pandemic situations, 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.

Medical and Surgical History

A complete medical and surgical history (which includes family history and UC-onset date) as well as history of tobacco and alcohol use, will be obtained from each subject from Study M11-290. Medical history will be updated at the Baseline Visit.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, body weight, and body temperature will be obtained at each visit. Blood pressure, pulse rate and respiratory rate should be performed before blood draws are performed. All measurements will be recorded in metric units if possible.

States of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to states of emergency or pandemic situations, subject visits may be conducted via phone or video conference. In these situations, vital signs (except weight) are not required but may be performed by the subject or caregiver as needed.

The vital signs collected at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

Annual TB testing

For subjects with a negative TB test at the Screening visit of parent Study M11-290, an annual PPD or QuantiFERON-TB Gold re-test will be required.

The TB test sample collected at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug). Annual TB screening will not be required for subjects who have been treated for latent or active TB or have had a positive TB test at any time (prior to the study, or testing performed at any time point during Study M11-290). For such subjects, annual evaluation by a physician for clinical signs/symptoms of active TB (including a directed TB history and physical exam including lungs, lymph nodes and skin) or newly identified TB risk factors will be required at Baseline, Weeks 48, 96, 144, 192, 240 and 288.

If one of the annual tests has a positive test result, the matter should be discussed with the medical monitor prior to starting any prophylaxis. A CXR may be required for evaluation of active TB.

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or the QuantiFERON®-TB Gold test (or equivalent) must be performed for subjects with a negative test at Screening visit including those with a prior history of Bacille Calmette-Guérin (BCG) administration at the time the subject reaches the scheduled visits: Baseline, Weeks 48, 96, 144, 192, 240 and 288.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case must be discussed with the AbbVie Medical Monitor.

For the PPD test:

- The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement (or as per local guidelines), when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The absence of induration should be recorded, as "0 mm," not "negative."
- If there are sites where the available testing materials are not accepted, an alternative tuberculin skin test may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.
- If QuantiFERON®-TB Gold (or equivalent) result is indeterminate, the test should be repeated with a fresh blood sample. If a repeat QuantiFERON®-TB Gold (or equivalent) result is indeterminate, this should be considered a positive test result and the case must be discussed with the AbbVie Medical Monitor.

In the event both a PPD test and QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test.

Newly initiated prophylactic treatment should be captured in the source documents and on the concomitant medications page in the CRF. Prior therapy should be captured in the appropriate medical history CRF.

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

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in

TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.

- A pulmonologist must review the results of the PPD skin test and the CXR and has to give his/her opinion about the eligibility of each subject to continue in the study. This opinion must be documented in writing in the subject's source documents.

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

Physical Examination

A full physical examination will be performed at Baseline, Weeks 48, 96, 144, 192, 240 and 288/Premature Discontinuation Visits. Symptom-based physical examinations will be performed at all other visits.

The physical exam performed at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

A physical exam will be performed at the designated study visits in Table 1.

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

Pregnancy Tests

A serum pregnancy test will be performed at the Baseline, Weeks 48, 96, 144, 192, 240 and 288/Premature Discontinuation Visits on all female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Investigator or who are of childbearing potential.

The serum pregnancy test collected during the Week 52 of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

At all other subsequently scheduled study visits, subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Investigator or are of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study. Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 2 at the Baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, 168, 192, 216, 240, 264, 288/Premature Discontinuation Visits. Blood draws should be performed after all clinical assessments and questionnaires, vital sign determinations are obtained and before study drug administration during a visit.

The Blood sample collected at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

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.

Measurements and Volume(s) of Blood Samples to Be Drawn are described in Appendix I.

Other Laboratory Assessments

hs-CRP

Blood samples for high-sensitivity C-Reactive Protein (hs-CRP) will be obtained at the Baseline, Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288/Premature Discontinuation Visits.

The Blood sample collected at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

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

Urinalysis

Urine samples will be obtained and sent to the central lab for the tests listed in Table 2 at the Baseline Weeks 4, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288/Premature Discontinuation Visits. Microscopic urinalysis will only be performed by the central laboratory if the dipstick UA results are abnormal, where abnormal is defined as a ketone, protein, blood or glucose value of greater than a trace.

The urine sample collected at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Albumin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides	Specific gravity Ketones pH Protein Glucose Blood **Others** High-sensitivity C-reactive protein (hs-CRP) β-HCG

States of Emergency or Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of states of emergency or pandemic situations 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. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug cannot be dispensed to the subject. The subject should be scheduled for laboratory draws as soon as feasible prior to the scheduled visit.

Bone Age

An x-ray of the wrist for the assessment of bone age will be obtained at Baseline; Weeks 48, 96, 144, 192, 240 and 288 visit to determine changes in bone maturation. Sites should use the Greulich and Pyle method for reading the x-ray.[21] The x-ray report requires the signature of the radiologist who read the films. The bone age that is determined by the x-ray should be recorded on the eCRF. Assessment of bone age will not be required for subjects at the Premature Discontinuation visit.

The x-ray collected at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug). If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age can be omitted.

Anthropometric Evaluations

Height and weight obtained at Baseline, Weeks 24, 48, 72 and 96, 144, 192, 240 and 288/Premature Discontinuation will be used by AbbVie Data Management and Statistical groups for determination of BMI and "z" score (observed height velocity [cm/yr] – mean height velocity for age and sex [cm/yr]/SD of the mean) for height.

At Baseline, height from the Week 52 visit of Study M11-290 will be used and maximal weight attained will be recorded.

Tanner Stage

Tanner Stage will be assessed at Baseline, Weeks 48, 96, 144, 192, 240 and 288/Premature Discontinuation Visit. Tanner Staging should be captured on the appropriate eCRF page. The Tanner Stage assessed at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

Pediatric Ulcerative Colitis Activity Index (PUCAI)

A PUCAI score will also be calculated at all study visits beginning at Baseline. The PUCAI score calculated at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

An example of the PUCAI is located in Appendix C.

The PUCAI score will be assessed using subject-reported symptoms and activity level. The answers should reflect symptoms and activity level during the previous 24 hours. The PUCAI scores of the last 2 days prior to each study visit will be averaged and used for the PUCAI scores for each study visit. The total PUCAI score will be rounded up to the next 5-point interval as applicable. In order to account for unavailable or excluded diary entries as per the provisions given below diary entries for the PUCAI score of the most recent 2 days within 10 days prior to each study visit will be used.

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

The subscore for the number of stools per 24 hours during days which a subject received anti-diarrheal medication will be scored as 15.

Mayo Score

All subjects will be provided with a Subject Diary at the Baseline Visit where they will record ulcerative colitis related symptoms. The Partial Mayo Score will be calculated from the subject diary at each visit beginning at Baseline. The average entry from the 5 days prior to each study visit will be used for each subject-reported subscore. In addition to the physical examination, the investigator should use the subject-reported

subscores of abdominal discomfort and functional assessment to determine the physician's global assessment subscore.

Normal number of bowel movement is the number of stools per day (24 hours) that is typical for the subject when having active UC but not experiencing a flare. Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.

The Mayo Score (consisting of the Partial Mayo Score plus the endoscopic subscore) will be calculated at weeks where endoscopy is performed (i.e., Week 48, 96, 192 and 288). The Partial Mayo Score and the Mayo Score (consisting of the Partial Mayo Score plus the endoscopic subscore) assessed at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug). The Mayo Score and the Script for collection of Mayo Score are described in Appendix D.

The average stool frequency subscore, rectal bleeding subscore, Partial Mayo score and Mayo score for each study visit will be recorded in the eCRF in decimal numbers.

For the purpose of disease flare assessment, Baseline PMS will be rounded up or down to the nearest full number. For example, *if a patient had a PMS of 5.4 at Baseline and came in for a disease flare assessment, then the Baseline PMS would be rounded down to 5.0 for this purpose. If a patient had a PMS of 5.5 at Baseline and came in for a disease flare assessment, then the Baseline PMS would be rounded up to 6.0.*

Whenever possible, the same physician (investigator or subinvestigator) should determine all Mayo Scores and Partial Mayo Scores for an individual subject through the duration of the study.

IMPACT III Questionnaire[22]

Subjects 9 years of age or older at Baseline will complete an IMPACT III questionnaire at Baseline, Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288/Premature Discontinuation Visit.

The IMPACT III questionnaire assessed at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

WPAI Questionnaire

Work Productivity and Activity Impairment Questionnaire (WPAI) will be completed at Baseline, Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288/Premature Discontinuation Visit (Appendix E). The WPAI questionnaire assessed at the Week 52 visit of Study M11-290 will be used for the Baseline assessment (prior to receiving study drug).

The subject's parent or legal guardian will complete the WPAI. The questionnaire will not be completed if the subject's parents or legal guardian do/does not take care of the subject anymore.

States of Emergency or Pandemic-Related Acceptable Protocol Modifications

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

Subject Diary/Dosing Log

Subjects will be dispensed an electronic diary at Baseline and will be trained on how to complete the diary by site staff during the Baseline 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 Week 288/Premature Discontinuation Visit.

Non-Drug Materials provided to the Study Sites are described in Appendix H.

Subjects will also be trained on how to complete the dosing log by site staff. Dosing log must be recorded each time a dose is administered. In the dosing log, the date and time study drug administration, the kit number, vial/syringe number and the dose administered will be recorded. At every site visit, the site staff will record subject's body weight and will inform the subject or his/her caregivers about the amount/dose of study drug to be administered each week until the next site visit.

The dosing records will be reviewed and verified for compliance at each visit by the research personnel at the study center and reinforced if necessary. All relevant dosing information will be retained by the study coordinator and transcribed onto a drug accountability form at each visit. Additionally, any discernible departure from the protocol regarding study drug administration will be recorded on the source documents and in the appropriate drug accountability form.

The subject should bring the subject diary/dosing log to every study visit.

Study Drug Dispensing/Administration

Study drug will be administered to all subjects by the subject or their designated family member or friend under the supervision of site medical staff to reinforce proper aseptic subcutaneous injection technique. Subjects or a trained designated family member or friend or will perform the injections of the study medication in the subject's home during the weeks when a clinic visit is not scheduled.

At all office visits, subjects should be observed after study drug administration until judged medically appropriate by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home

subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

Subjects should administer study medication on the same day of the week. The dosing dates for all doses of study drug should be calculated from the Baseline visit date. A ± 3-day window is allowable for scheduled study dosing dates. For subjects that deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the ± 3-day window, please contact the AbbVie Medical Monitor for additional instructions.

Study drug kits will be assigned by the IRT. Since the amount of study drug that subject gets based on subject's body weight, at every site visit, study personnel will record subject's weight and will inform subject the amount/dose of study drug to be administered.

States of Emergency or Pandemic-Related Acceptable Protocol Modifications

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
- Study drug can be administered by the subject (or subject's caregiver) at home
- 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 states of emergency or pandemic related social distancing, this may

be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

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

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents. AbbVie will submit any required notifications to the regulatory authority as applicable.

Body Weight Adjusted Volumes of Study Drug for Administration of Open Label Adalimumab 0.6 mg/kg Dosing (Weight Based) prior to Amendment 4 are described in Appendix F.

Subjects will be instructed to return all used and unused vials/syringes, Sharps containers and empty boxes at each visit for accountability.

Injections during subsequent study visits will be performed at the site by the subject or their designated family member or friend under the supervision of site medical staff to reinforce proper aseptic subcutaneous injection technique. Subjects or a trained designated family member or friend or will perform the injections of the study medication in the subject's home during the weeks when a clinic visit is not scheduled.

Endoscopy (Optional)

An endoscopy may be performed at the discretion of the investigator on the following occasions:

- Week 48
- Week 96
- Week 192
- Week 288/Premature Discontinuation

In this case, endoscopies may be either flexible sigmoidoscopy or colonoscopy.

Note:

- Biopsies to rule out malignancy, dysplasia, colon cancer or infection may be taken at the investigator's discretion.

The evaluation of endoscopies will be done by usage of the endoscopy subscore scale of the Mayo score and will include an assessment of friability.

5.3.2 Efficacy Variables

This study will utilize the PMS (and Mayo score if available) and PUCAI to determine efficacy of the study drug.

The following efficacy endpoints will be analyzed using summary statistics:

- The proportion of subjects who achieve clinical remission as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1) over time;
- The proportion of subjects who achieve clinical response as measured by PMS (defined as a decrease in PMS ≥ 2 points and $\geq 30\%$ from Study M11-290 Baseline) over time;
- The proportion of subjects who achieve PUCAI remission (defined as < 10) over time;
- The proportion of subjects who achieve PUCAI response (defined as a decrease in PUCAI ≥ 20 points from Study M11-290 Baseline).

Efficacy will also be evaluated based on other measures of disease activity, including IMPACT III, WPAI, z-score for height and weight, bone age, BMI, and laboratory values as applicable. The proportion of subjects who achieve remission/response based on Mayo score and mucosal healing based on Mayo endoscopy subscore will be summarized for subjects with available Mayo score.

5.3.3 Safety Variables

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

5.3.4 Pharmacokinetic Variables

Pharmacokinetic and Immunogenicity:

Blood samples for serum adalimumab concentrations and immunogenicity status collected prior to Amendment 2 will be maintained for potential analysis of serum adalimumab and AAA concentrations. As appropriate, population pharmacokinetic analysis and/or any additional analyses may be performed.

Samples collected prior to Amendment 2 will be stored in a secure storage space with adequate measures to protect confidentiality. The samples may be retained for up to 5 years (where allowed by local guidelines) after completion of the study research. Samples that are not analyzed will be discarded by the end of the 5-year period specified above.

5.3.4.1 Cytokines and Serologic Variables

Samples collected prior to Amendment 2 may be analyzed for serologic antibodies and cytokines that may help predict disease behavior and help determine disease phenotypes or response to or tolerability of treatment. Some antibodies or immune markers insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may also be used for the development of diagnostic tests. The results of analyses will not be reported with the study summary.

Samples collected prior to Amendment 2 will be stored in a secure storage space with adequate measures to protect confidentiality. The samples may be retained for up to 5 years (where allowed by local guidelines) after completion of the study research.

Samples that are not analyzed will be discarded by the end of the 5-year period specified above.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor (see Section 5.2 and Section 6.1.7).
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- Subject is diagnosed with a malignancy, except for localized non-melanoma skin cancer. Discontinuation for dysplasia or carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.

- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie Medical Monitor.

States of Emergency or Pandemic-Related Acceptable Protocol Modification

During states of emergency or pandemic situations, 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 throughout the protocol.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a state of emergency or pandemic related reason to ensure all acceptable mitigation steps have been explored.

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

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may

be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Termination Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final phone call will be made to the subject at least 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

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

5.4.2 Discontinuation of Entire Study

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

This study may conclude approximately 12 weeks after one of the following criteria have been satisfied:

- Study drug received country and local (if applicable) regulatory approval for pediatric ulcerative colitis and application for local reimbursement has been submitted.
- The Sponsor determined that continuation of the study does not further promote the scientific objective of the study.

Following site notification of upcoming conclusion of study, subjects should return to their next scheduled study visit as specified in the protocol. The termination visit should be conducted in place of their regular scheduled study visit. These subjects are considered as having completed the study.

5.5 Treatments

5.5.1 Treatments Administered

Prior to Amendment 4, all subjects received open-label therapy as follows beginning at the Baseline Visit in Study M10-870:

- Subjects who enrolled into the study from blinded treatment in Study M11-290 were to receive open label 0.6 mg/kg (maximum of 40 mg) eow of adalimumab.
- Subjects who received open label adalimumab in Study M11-290 were to maintain the same dose in Study M10-870.

After Amendment 4, ongoing subjects will be switched to receive a fixed dose regimen, by weight cutoff, incorporating open-label citrate free adalimumab in PFS (20 mg, 40 mg, or 80 mg) as follows:

- Subjects with a body weight < 25 kg will receive open label 20 mg eow of adalimumab

- Subjects with a body weight ≥ 25 kg - < 40 kg will receive open label 40 mg eow of adalimumab
- Subjects with a body weight ≥ 40 kg will receive open label 80 mg eow of adalimumab

Treatment of Subjects with Disease Flare

Prior to Amendment 4:

- Subjects who were on 0.6 mg/kg (maximum dose of 40 mg, weight based) eow of adalimumab could receive 0.6 mg/kg (maximum of 40 mg, weight based) ew.
- Subjects who were on 0.6 mg/kg ew of adalimumab could receive 40 mg ew (maximum dose) of adalimumab.

Subjects with persistently uncontrolled disease while on adalimumab 40 mg ew (max dose) were to be discontinued from the study.

After Amendment 4:

- Subjects who are on 20 mg eow of adalimumab may receive 40 mg eow of adalimumab.
- Subjects who are on 40 mg eow of adalimumab may receive 80 mg eow of adalimumab.

Subjects with persistently uncontrolled disease while on adalimumab 80 mg eow should be discontinued from the study.

Consideration should be given to have the subject return to the study site for unscheduled visit in order to collect the required PMS to satisfy the definition of disease flare.

Criteria for Disease Flare are as follows:

- Subjects with a Baseline Study M10-870 PMS of 0 to 2 who present with a PMS at least 3 points greater than their Baseline Study M10-870 score.
- Subjects with a Baseline Study M10-870 PMS of 3 to 4 who present with a PMS at least 2 points greater than their Baseline Study M10-870 score.
- Subjects with a Baseline Study M10-870 PMS of 5 to 6 who present with a PMS at least 1 point greater than their Baseline Study M10-870 score.
- Subjects who present with a PMS at the current visit of at least 2 points greater than their PMS at the previous visit and who are not in remission per PMS.

Subjects who have been in remission (PMS $\leq$ 2 with no individual subscore > 1) for at least 8 weeks and for at least 2 consecutive visits may have their dosage de-escalated from ew to eow prior to Amendment 4 or to the next lower dose after Amendment 4. The investigator should receive prior approval from the Medical Monitor before taking any action with regard to dose de-escalation.

If subjects demonstrate disease flare after dose de-escalation, subjects also have an opportunity to re-escalate their dose back to adalimumab ew dosing prior to Amendment 4 or to the next higher dose after Amendment 4. The investigator should receive prior approval from the Medical Monitor before taking any action with regard to dose re-escalation. One de-escalation within a period of 48 weeks and one re-escalation within a period of 48 weeks are permissible.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3.

Table 3. Identity of Investigational Products

Study Drug	Mode of Administration	Presentation	Strength	Manufacturer
Adalimumab	Subcutaneous injection	Vial or pre-filled syringe	Vial: 40 mg/0.8 mL Pre-filled Syringe: 20 mg/0.2 mL, 40 mg/0.4 mL, and 80 mg/0.8 mL	AbbVie

5.5.2.1 Packaging and Labeling

All Treatment Types

Investigational product will be packaged separately in cartons containing either vials or pre-filled syringes. Each dosing kit carton will have a unique kit ID and contains two labeled vials or syringes. Each vial/syringe and kit will be labeled per local regulatory requirements.

All labels must remain affixed to study medication at all times, and should never be removed for any reason.

Detailed list of study supplies are provided in Appendix H.

5.5.2.2 Storage and Disposition of Study Drug

Adalimumab vials/syringes are to be stored protected from light at 2°C to 8°C/36°F to 46°F. Study medication drug must not be frozen at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded every business day on a temperature log to record proper function. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study medication should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie or destroyed at the site in accordance with local regulations and per instructions from AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

Subjects who meet the selection criteria in Section 5.2.1 and Section 5.2.2 will proceed to enter the study. This is an open-label study, therefore, subjects will not be randomized. Subjects will keep their study subject number from the previous Study M11-290. The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IRT. Before the study is initiated, the telephone number and call-in directions for the IRT will be provided to each site.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

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

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

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

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study. The study drug must not be used for reasons other than that described in the protocol.

The subject or their qualified designee will administer all doses of study drug. Appropriate site staff will supervise the subject's administration of the study drug at required in-office study visits to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a subject diary/dosing log to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. If the subject does not bring the subject diary/dosing log to the site visit and does not return used and unused vials/syringes, IP boxes and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The 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.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the subject diary/dosing log is returned before completing on the applicable eCRF page.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, (in the US/Puerto Rico adequate temperature is cool to the touch,

OUS US/Puerto Rico temperature recording devices [templates] are provided in the shipments) and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the site on a Site Drug Accountability log including date received, the lot number, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug.

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

5.6.2 Appropriateness of Measurements

The design of this clinical trial was chosen to demonstrate adalimumab as an effective and safe therapy in pediatric subjects with moderately to severely active UC who completed the Study M11-290. At Baseline, all subjects will receive open-label therapy.

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The clinical efficacy measurements in this study (Partial Mayo Score and PUCAI) are commonly used for assessing disease activity in clinical studies in subjects with UC. All clinical and laboratory procedures in this study are standard or generally accepted.

5.6.3 Suitability of Subject Population

Pediatric subjects with moderately to severely active UC who completed the Study M11-290. The specific subject population chosen was based on unmet medical needs of currently available medical therapies as well as previous anti-TNF studies that demonstrated effectiveness in UC.

5.6.4 Selection of Doses in the Study

Doses were selected using a population pharmacokinetic model of adalimumab using data from pediatric and adult subjects with Crohn's disease (Study M06-806 and Study M02-433, respectively) and adult subjects with ulcerative colitis (Study M06-827). Because UC disease was not a significant covariate on CL/F and V/F, and literature suggests that the demographic characteristics of pediatric subjects with CD and UC are similar, simulations were conducted using this PK model and demographic data from the pediatric CD study, Study M06-806, including age, weight, albumin concentrations and AAA rates.

In consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation both treatments provided evidence of

efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with UC the study design provides investigators with the option of dose de-escalation by reducing the dose (after Amendment 4) or switching from ew to eow (prior to Amendment 4) based on the clinical status of the individual patient.

The selected fixed-dose regimen after Amendment 4 is supported by modeling and simulation results generated with the final PK model with data from Study M11-290 and is aligned with the dosing per recently-approved and anticipated global labeling. Modeling and simulation analysis predicted largely overlapping concentration-time profiles in pediatric subjects with UC for the selected fixed-dose regimen and the respective mg/kg dosing studied in Study M11-290. In addition, logistic regression analysis demonstrated comparable probability of achieving the Week 52 co-primary efficacy endpoint for the fixed-dose regimen and the mg/kg eow or ew dosing, respectively.

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 after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2). For adverse events, please refer to Sections 6.1.1 and 6.1.7. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

6.1.1 Definitions

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record

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

All adverse events will be followed to a satisfactory conclusion.

6.1.2 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention (see Section 6.7 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.

6.1.3 Serious Adverse Events

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

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

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

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

6.1.4 Adverse Event Severity

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

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

6.1.5 Relationship to Study Drug

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

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

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

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

6.1.6 Adverse Event Collection Period

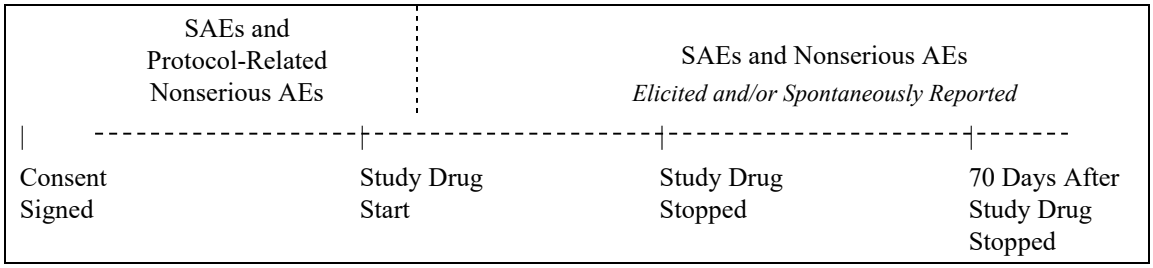
All adverse events reported from the time of study drug administration until 70 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse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

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

There may be instances where a 70-day follow-up phone call occurs after the locking of the clinical database. In this situation, any adverse events reported to AbbVie from this 70-day follow-up phone call will be evaluated for inclusion in the clinical database. All SAEs or adverse events of special interest, as defined by AbbVie, reported during the 70-day follow-up phone call must be captured in the clinical database.

Adverse event information will be collected as shown in Figure 1.

Figure 1. Adverse Event Collection



6.1.7 Adverse Event Reporting

In the event of a serious adverse event, whether related to 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 RAVE® 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 emailed (preferred route) to Clinical Pharmacovigilance within 24 hours of being made aware of the 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, Bldg. AP31
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Safety Hotline: (847) 938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

Primary Therapeutic Area Physician:

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

Telephone Contact Information:
Phone:
Fax:
Cell:
Email: [redacted]

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

Phone: +1 (973) 784-6402

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

COVID-19 Pandemic-Related Instructions

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.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All AEs associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 vaccine eCRF.

6.1.8 Pregnancy

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

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

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

6.2 Product Complaints

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

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

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

6.2.1 Definitions

A Product Complaint is any Complaint (see Section 6.2 for the definition) related to the biologic or drug component of the product or to the medical device component(s), if present (see below).

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.

6.3 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 6.1.3 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable) including those that may be due to the states of emergency or pandemic situations and the following AbbVie Representative:

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

Telephone Contact Information:
Phone:
Fax:
Cell:
Email: [redacted]

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
- DTP shipments

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of adalimumab for the maintenance of clinical remission in pediatric subjects with moderately to severely active ulcerative colitis. Complete, specific details of the

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

8.1.1 Analyzable Population

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

The safety population for analysis of safety and the ITT population for evaluation of efficacy endpoints are identical and include all subjects who received at least one dose of adalimumab in Study M10-870.

8.1.2 Planned Methods of Statistical Analysis

All statistical analysis results will be reported using descriptive statistics. Descriptive summary statistics will be provided for the demographic and Baseline characteristics, efficacy, and safety parameters. Continuous variables will be summarized using the number of observation, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized using count and percentages. For dichotomized efficacy variables, data will be summarized by number and percent of subjects with 95% confidence interval.

8.1.3 Demographics and Baseline Characteristics

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind Study M11-290).

8.1.4 Efficacy Analysis

Summary statistics will be provided for each visit, based on observed data and non-responder imputation (NRI) for missing categorical data. An additional summary will be provided for the last visit, using the last observation carried forward (LOCF). That is, the subject's last non-missing, post-Baseline value (i.e., post-Week 52 Study M11-290 value) will be carried forward to the last visit. Details will be provided in the Statistical Analysis Plan (SAP).

8.1.5 Statistical Analyses of Safety

Treatment emergent AEs, serious adverse events (SAEs), and AEs of special interest will be summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. A summary of AEs by severity and relationship to study drug will be performed. Other safety variables such as laboratory and vital sign data will be described by descriptive statistics. In addition, shift tables and listings will be provided.

8.1.6 Other Analyses

Details of subgroup analysis and all other analyses will be provided in the SAP.

8.1.7 Interim Analysis

An interim analysis on safety and efficacy will be performed and reported in a full Interim Clinical Study Report for inclusion of the Study M10-870 data in the submission of applications for regulatory approval of the pediatric UC indication in conjunction with the Study M11-290 results. An interim analysis will be conducted after the last subject completed or discontinued from the M11-290 main study. Additional interim analyses may be performed, as needed.

8.2 Determination of Sample Size

Subjects who successfully completed Study M11-290 through Week 52 may be eligible to participate in this study. Based on an expected number of 155 subjects being re-randomized at Week 8 of the parent study, an expected Study M11-290 completion rate of 66% and a roll-over rate of 80% of eligible subjects (based on previous experience with the pediatric CD Studies M06-806 and M06-807) it is expected that approximately 85 subjects from Study M11-290 will enroll into the main study globally and 8 subjects from the Japanese sub-study.

8.3 Randomization Methods

All subjects will be centrally registered using an IRT system. This is an open-label study; therefore, subjects will not be randomized. Before the study is initiated, the IRT log-in details will be provided to each site. Subjects will keep their subject number from the previous study (Study M11-290).

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.

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 or pandemic situations 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. 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 the subject's parent/legal guardian, and answer all questions regarding this study. Pediatric subjects will be included in all discussions in order to obtain verbal or written assent. Prior to any study-related procedures being performed on the subject, the informed consent statement will be reviewed and 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 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.

Non-genetic biomarker analysis will only be performed if the subject's parent/legal guardian has voluntarily signed and dated a separate non-genetic biomarker informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject and subject's parent/legal guardian has had an opportunity to ask questions. The separate non-genetic biomarker informed consent must be signed before the non-genetic biomarker testing is performed. If the subject's parent/legal guardian does not consent to the non-genetic biomarker testing, it will not impact the subject's participation in the study.

A copy of the informed consent 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.

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

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

The following assessments that will be completed by the subject and/or subject's parent/legal guardian or physician will be considered source documentation:

- IMPACT III
- WPAI: UC – Caregiver

The adverse event electronic data capture case report form (eCRF) data segments of: alternate etiology, severity, frequency and relationship to study drug, may also be used as source and will require an Investigator approval on the eCRF as verification of the accuracy of the information.

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 states of emergency or pandemic situations, 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 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, except for subject-completed questionnaires, which will be completed on paper by the subject then transcribed into the EDC system. All data entered into the eCRF will be supported by source documentation.

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

Patient Reported Outcomes (PRO) data is collected directly onto paper CRFs by the subjects. The completion of these forms is verified by the site staff. The forms are entered into the clinical database and then can be viewed within the EDC system by the site staff.

All questionnaires must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, the date of the correction, the reason for the correction, and the initials of the person making the correction. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry.

10.3 Electronic Patient Reported Outcomes (ePRO)

Subject reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome

(ePRO) tool called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO tool is available through the vendor, CRF Health, while the user acceptance testing of the study-specific ePRO design will be conducted and maintained at AbbVie.

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

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

The ePRO data (such as stool frequency, rectal bleeding, abdominal discomfort, and general well-being) will be collected electronically via a handheld device into which the subject will record the required pieces of information on a daily basis. In addition, study drug administration data (such as kit number, vial/syringe number and amount/dose administered) will be collected electronically via a handheld device into which the subject will record this required information on a weekly basis. The electronic device will be programmed to allow data entry for throughout the day. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

10.4 Data Collection Process

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

11.0 Data Quality Assurance

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 adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, to the FDA and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

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

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

14.0 Investigator's Agreement

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

Protocol Title:	A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Ulcerative Colitis Who Completed the Study M11-290
Protocol Date:	04 August 2021

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Griffiths AM. Specificities of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol. 2004;18(3):509-23.
2. Biancone L, Michetti P, Travis S, et al; European Crohn's and Colitis Organisation (ECCO). European evidence-based consensus on the management of ulcerative colitis: special situations. J Crohns Colitis. 2008;2(1):63-92.
3. Kappelman MD, Grand RJ. Does inflammatory bowel disease develop in infants? Inflamm Bowel Dis. 2008;14 (Suppl 2):S6-8.
4. Hassan K, Cowan FJ, Jenkins HR. The incidence of childhood inflammatory bowel disease in Wales. Eur J Pediatr. 2000;159(4):261-3.
5. Lakatos L, Mester G, Erdelyi Z, et al. Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of western Hungary between 1977-2001. World J Gastroenterol. 2004;10(3):404-9.
6. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child. 2003;88(11):995-1000.
7. Auvin S, Molinié F, Gower-Rousseau C, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988-1999). J Pediatr Gastroenterol Nutr. 2005;41(1):49-55.
8. Armitage E, Drummond HE, Wilson DC, et al. Increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland. Eur J Gastroenterol Hepatol. 2001;13(12):1439-47.
9. Hildebrand H, Finkel Y, Grahnquist L, et al. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990-2001. Gut. 2003;52(10):1432-4.
10. Karolewska-Bochenek K, Lazowska-Przeorek I, Albrecht P, et al. Epidemiology of inflammatory bowel disease among children in Poland. A prospective, population-based, 2-year study, 2002-2004. Digestion. 2009;79(2):121-9.

11. Everhart JE. The Burden of Digestive Diseases in the United States. In: Everhart JE, editor. Inflammatory Bowel Disease. Washington DC: US Government Printing Office; 2008. p. 97-106.
12. Ruter 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.
13. Kornbluth A, Sachar DB. Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2004;99(7):1371-85.
14. Hyams JS, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10(4):391-9.e1.
15. Humira® (adalimumab) [package insert]. North Chicago, IL; AbbVie, 2011.
16. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60(6):780-7.
17. Reinisch W, Sandborn WJ, Kumar A, et al. 52-week clinical efficacy with adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Gut. 2011;60:A139-40.
18. Sandborn WJ, Van Assche G, Reinisch W, et al. Induction and maintenance of clinical remission by adalimumab in patients with moderate-to-severe ulcerative colitis. J Crohns Colitis. 2011; (5 Suppl 1):S68. Abstract P136.
19. Sandborn WJ, Van Assche G, Thakkar RB, et al. Adalimumab improves health-related quality of life for 52 weeks in patients with ulcerative colitis. J Crohn's Colitis. 2011; (5 Suppl 1):S87, P181.
20. Haberman R, Axelrad J, Chen A, et al. Covid-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. N Engl J Med. 2020;383(1):85-8.

21. Greulich WW, Pyle S, Idell ST. Radiographic Atlas of Skeletal Development of the Hand and Wrist. Am J Med Scis. 1959;238(3):261-396.

22. Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2002;35(4):557-63.

23. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133(2):423-32.

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

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

Appendix 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]	Statistics
		Clinical
		Pharmacokinetics
		Clinical
		Clinical
		Clinical

Appendix C. Pediatric Ulcerative Colitis Activity Index (PUCAI)

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in < 50% of stools	10
Small amount with most stools	20
Large amount (> 50% of stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. Number of stools per 24 hours	
0-2	0
3-5	5
6-8	10
> 8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
TOTAL MAXIMUM SCORE	**85**

The Pediatric Ulcerative Colitis Activity Index (PUCAI)[23] is the copyright of The Hospital for Sick Children, Toronto, Canada, authored by Dr. Anne Griffiths, Dr. Dan Turner and Dr. Anthony Otley. The PUCAI will be provided under license from The Hospital for Sick Children and must not be copied, distributed or used in any way without the prior written consent of The Hospital for Sick Children.

Appendix D. Mayo Scoring System

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

Stool Frequency Subscore 0 = Normal 1 = 1 – 2 stools/day more than normal 2 = 3 – 4 stools/day more than normal 3 = > 4 stools/day more than normal Each subject serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal Bleeding Subscore 0 = None 1 = Visible blood with stool less than half the time 2 =Visible blood with stool half of the time or more 3 = Passing blood alone A score of 3 for bleeding requires subjects to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.
Endoscopy Subscore: 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment Subscore 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

Adapted from Schroeder KW, et al, and Lewis JD, et al.[24,25]

Script for Collection of Mayo Scores

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

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

Stool Frequency Subscore

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

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

- A number of bowel movements lower than or equal to the normal number of bowel movements should be scored as 0 = Normal.
- One or 2 bowel movements more than the normal number of bowel movements should be scored as 1.
- Three or 4 bowel movements more than the normal number of bowel movements should be scored as 2.
- Five or more bowel movements more than the normal number of bowel movements should be scored as 3.

The Stool Frequency subscores from the 5 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit. In order to account for unavailable or excluded diary entries as per the provisions given below diary entries of the most recent 5 days within 14 days prior to each study visit will be used.

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

Rectal Bleeding Subscore

Subjects should record a daily rectal bleeding subscore value as follows:

- No visible blood with stool during the respective day should be scored as 0.
- Visible blood with stool less than half the time during the respective day should be scored as 1.
- Visible blood with stool at least half the time during the respective day should be scored as 2.
- A score of 3 for bleeding requires subjects to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

The score entries into subject's diary from the 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit. In order to account for unavailable or excluded diary entries as per the provisions given below diary entries of the most recent 5 days within 14 days prior to each study visit will be used.

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

Physician's Global Assessment Subscore

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

- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

Endoscopy Subscore

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

- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

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

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

Appendix E. Work Productivity and Activity Impairment Questionnaire: Ulcerative Colitis V2.0 (WPAI: UC) – Caregiver

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

1. Are you currently employed (working for pay)? _____ NO _____ YES

   If NO, check "NO" and skip to question 6.

   The next questions are about the past 7 days, not including today.

2. During the past 7 days, how many hours did you miss from work because of problems associated with your child's ulcerative colitis? Include hours you missed on sick days, times you went in late, left early, etc., because of your child's ulcerative colitis. Do not include time you missed for your child to participate in this study.

   _____HOURS

3. During the past 7 days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off for your child to participate in this study?

   _____HOURS

4. During the past 7 days, how many hours did you actually work?

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

5. During the past 7 days, how much did your child's ulcerative colitis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your child's ulcerative colitis affected your work only

a little, choose a low number. Choose a high number if your child's ulcerative colitis affected your work a great deal.

Consider only how much your child's ulcerative colitis affected productivity while you were working.

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

CIRCLE A NUMBER

6. During the past 7 days, how much did your child's ulcerative colitis affect your ability to do your regular daily activities, other than work at a job?

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

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

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

CIRCLE A NUMBER

WPAI:UC – Caregiver V2.0 (US English)

Appendix F. Body Weight Adjusted Volumes of Study Drug for Administration of Open Label Adalimumab 0.6 mg/kg Dosing (Weight Based)

Weight (kg)	Administered (# of vial used)	Volume (mL)	Weight (Kg)	Administered (# of vial used)	Volume (mL)	Weight (kg)	Administered (# of vial used)	Volume (mL)
14	1×	0.17	36	1 x	0.43	58	1×	0.70
15	1×	0.18	37	1 x	0.44	59	1×	0.71
16	1×	0.19	38	1 x	0.46	60	1×	0.72
17	1×	0.20	39	1 x	0.47	61	1×	0.73
18	1×	0.22	40	1 x	0.48	62	1×	0.74
19	1×	0.23	41	1 x	0.49	63	1×	0.76
20	1×	0.24	42	1 x	0.50	64	1×	0.77
21	1×	0.25	43	1 x	0.52	65	1×	0.78
22	1×	0.26	44	1 x	0.53	66	1×	0.79
23	1×	0.28	45	1 x	0.54	67	1×	0.80
24	1×	0.29	46	1 x	0.55	68	1×	0.80
25	1×	0.30	47	1 x	0.56	69	1×	0.80
26	1×	0.31	48	1 x	0.58	70	1×	0.80
27	1×	0.32	49	1 x	0.59	71	1×	0.80
28	1×	0.34	50	1 x	0.60	72	1×	0.80
29	1×	0.35	51	1 x	0.61	73	1×	0.80
30	1×	0.36	52	1 x	0.62	74	1×	0.80
31	1×	0.37	53	1 x	0.64	75	1×	0.80
32	1×	0.38	54	1 x	0.65	76	1×	0.80
33	1×	0.40	55	1 x	0.66	77	1×	0.80
34	1×	0.41	56	1 x	0.67	78	1×	0.80
35	1×	0.42	57	1 x	0.68	79	1×	0.80
						80	1×	0.80

Appendix G. 70-Day Follow-Up Call – Sample

Site Name/Number: _____

Subject Number: _____

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

Date of Call: _____

- ☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least three attempts.)
- ☐ No Events Reported

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

_____

_____

_____

_____

_____

_____

Appendix H. Non-Drug Materials Provided to the Study Sites

Study sites will receive the following supplies prior to or during the study for distribution to subjects:

Tote Bags

Coolers

Gel Packs

Subject Diaries

Sharps Containers

Appendix I. Measurements and Volume(s) of Blood Samples to Be Drawn

The measurements and volume(s) of blood samples to be drawn at the time point indicated in the table below:

Visit	Measurement	Volume (mL)	Total Blood Volume (mL)/Visit
Baseline samples Drawn at Week 52 Study M11-290	Chemistry, hCG*, hsCRP	2.5	7.5**
	Hematology	2.0	
	QuantiFERON TB Gold	3.0	
Week 4	Chemistry, hCG*	2.5	4.5
	Hematology	2.0	
Week 8	hCG*	2.5	2.5
Week 12	Chemistry, hCG*	2.5	4.5
	Hematology	2.0	
Week 24	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 36	Chemistry, hCG*,	2.5	4.5
	Hematology	2.0	
Week 48	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	7.5
	QuantiFERON TB Gold^	3.0	
Week 60	Chemistry, hCG*	2.5	4.5
	Hematology	2.0	
Week 72	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 84	Chemistry, hCG*	2.5	4.5
	Hematology	2.0	
Week 96	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	7.5
	QuantiFERON TB Gold^	3.0	
Week 108	Chemistry, hCG*,	2.5	4.5
	Hematology	2.0	

Visit	Measurement	Volume (mL)	Total Blood Volume (mL)/Visit
Week 120	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	4.5
Week 144	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	7.5
	QuantiFERON TB Gold^	3.0	
Week 168	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 192	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	7.5
	QuantiFERON TB Gold^	3.0	
Week 216	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 240	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	7.5
	QuantiFERON TB Gold^	3.0	
Week 264	Chemistry, hCG*, hsCRP	2.5	4.5
	Hematology	2.0	
Week 288/ Premature	Chemistry, hCG*, hsCRP	2.5	
Discontinuation	Hematology	2.0	7.5
	QuantiFERON TB Gold^	3.0	
Unscheduled Visit	Chemistry, hCG*, hsCRP	2.5	
	Hematology	2.0	4.5
	Total		101.5

* Only performed in female of childbearing potential that has positive urine pregnancy test.

** At the Baseline visit, the blood samples for Study M10-870 will be completed as part of Week 52 of the Study M11-290 protocol and blood volume is not used to calculate the total blood volume for Study M10-870.

^ Subjects will not have the QuantiFERON test performed if a PPD test is used. For subjects with a negative TB test, a TB test will be required at Week 48, 96, 144, 192, 240 and 288. An annual TB screen testing will not be required for subjects who have been treated for latent or active TB or have had a positive TB test at any time (prior to the study, or testing performed at any time point during the Study M11-290).