1.0 Title Page

Clinical Study Protocol M14-347

A Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease

Incorporating Amendments 1 and 2

AbbVie Investigational Product:	Adalimumab
Date:	04 December 2014
Development Phase:	3
Study Design:	Phase 3, Multicenter, Open-label, Efficacy and Safety Study
EudraCT Number:	2013-004034-15
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor*:	[redacted]
Sponsor/Emergency Contact:	

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

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

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is as follows:

- Update synopsis to reflect Amendment Changes below.
- Update definition of Inadequate Response in Section 5.1.

  Rationale for change: to allow for subjects to escalate without the need to have results from two visits.
- Update the first week subjects are allowed to dose escalate in Section 5.1.

  Rationale for change: to clarify the point in the study subjects are first able to dose escalate.
- Remove serological biomarkers/mRNA testing, Abdominal Pain Rating Scale, and IBDQ, EQ-5D, and WPAI questionnaires from "Unscheduled Visit" in Table 2.

  Rationale for change: to clarify which activities are required at an unscheduled visit.
- Updated table note "k." for Table 2.

  Rationale for change: to clarify which visits are considered unscheduled visits.
- Update the Urinalysis subsection in Section 5.3.1.1.

  Rationale for change: to clarify when a microscopic analysis will be performed.
- Update Other Laboratory Assessments subsection in Section 5.3.1.1.

  Rationale for change: to clarify the time in which all stool samples should be returned to the site.
- Update Additional Efficacy Variables in Section 5.3.3.2.

  Rationale for change: to reflect changes made in Section 5.1 concerning the time in which subjects can be dose escalated if criteria are met.
- Update Section 5.2.3.2 with new contact information.

  Rationale for change: there is a change in the Secondary Study Designated Physician and an addition of a back-up 24/7 contact number for medical emergencies and safety concerns.

- Update typographical grammatical errors throughout protocol.

An itemized list of all protocol amendment changes can be found in Appendix M.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-347
Name of Study Drug: Adalimumab	**Phase of Development:** 3
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 04 December 2014
Protocol Title: A Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease	
Objectives: The primary objective of this study is to evaluate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in subjects with Crohn's disease (CD) who participated in and successfully completed Study M14-115. The secondary objective is to assess pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) administration.	
Investigators: Multicenter	
Study Sites: Only sites that have enrolled subjects from Study M14-115 will be included.	
Study Population: Subjects with CD who previously participated in and successfully completed Study M14-115.	
Number of Subjects to be Enrolled: Approximately 300 subjects who participated in and successfully completed Study M14-115.	
Methodology: This is an open-label extension (OLE) study which comprises a 40-week open-label period designed to evaluate the long-term efficacy, safety, and tolerability of adalimumab. Approximately 300 subjects with CD who participated in and successfully completed Study M14-115 will be enrolled. Subjects will be evaluated for entry into Study M14-347 at the final study visit (Week 12) of Study M14-115. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in this study. The Week 12 visit of Study M14-115 will be considered Week 0 (Baseline) of Study M14-347. All subjects will receive open-label adalimumab 40 mg every other week (eow) beginning at Week 0. Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 1 should the subject meet the criteria for inadequate response: **Inadequate Response:** Crohn's disease activity index (CDAI) $\geq$ 200 at any one visit and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP $\geq$ 5 mg/L. The hs-CRP results used to determine inadequate response can be from the prior or current visit. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.	

Methodology (Continued):

For subjects taking corticosteroids at Baseline of Study M14-115, adalimumab dose escalation should be considered in lieu of increases in steroid dose. Subjects who continue to experience inadequate response on 40 mg ew who were taking corticosteroids at Baseline may have their steroid dose increased, per the Investigator's discretion, in order to manage the subject's symptoms. Any subject who continues to experience inadequate response on 40 mg ew may be discontinued from the study at the investigator's discretion after discussion with the Study designated physician (SDP). Subjects who dose escalated to adalimumab 40 mg ew, have **one** opportunity to de-escalate adalimumab dose to 40 mg eow provided the following criteria have been met: CDAI < 200, and high-sensitivity C-reactive protein (hs-CRP) value equal to or lower than that observed at the time of dose escalation. Subjects who experience inadequate response after dose de-escalation (using the same criteria outlined above) may again be escalated to 40 mg ew. A subject has only **one** opportunity to dose-de-escalate and one opportunity to re-escalate to ew adalimumab dosing.

Study visits for clinical and safety assessments will be performed at Weeks 0, 8, 16, 24, 32 and 40/Premature Discontinuation (PD). All subjects will be provided a paper subject diary in which they will record CD-related symptoms (number of liquid or very soft stools, abdominal pain rating, general well-being) and adalimumab dosing information throughout the study. Blood samples will be collected at various timepoints for hs-CRP, adalimumab serum concentrations, anti-adalimumab antibody (AAA) levels and other biomarker analyses. In addition, stool samples for calprotectin and microbiota will be collected. The stool samples should be taken before starting bowel preparations for endoscopy. Endoscopic evaluation will be performed at Week 40/PD if the PD occurs after Week 24. CDAI evaluations will be calculated based on entries recorded into the subject's diary at all study visits. The SFPS (Stool [liquid/soft] Frequency + Abdominal Pain Score) will be calculated using the weighted values for the CDAI components "Number of liquid or very soft stools" and "Abdominal pain." Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject must have successfully enrolled in and completed Study M14-115, including the Week 12 ileocolonoscopy.
2. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
   - Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS)
   - Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
   - A vasectomized partner
   - Hormonal contraceptives for at least 90 days prior to study drug administration

   Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol 0.5 mg are not considered adequate

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

Main Inclusion (Continued):

3. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
4. Subject must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

Main Exclusion:

1. For any reason subject is considered by the investigator to be an unsuitable candidate.
2. Known hypersensitivity to adalimumab or its excipients.
3. Subject with an active systemic viral infection, or any active viral infection, that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
4. Positive pregnancy test at Baseline (Week 12 of Study M14-115).
5. Female subject who is considering becoming pregnant during the study.
6. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma and/or localized carcinoma in situ of the cervix. If the Week 12 (Study M14-115) colonoscopy shows evidence of dysplasia or a malignancy, subject must not be enrolled in the study.
7. Subject with a poorly controlled medical condition, such as uncontrolled diabetes, unstable ischemic heart disease, moderate or severe congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the investigator or sponsor, would put the subject at risk by participation in this study.
8. Subject is not in compliance with prior and concomitant medication requirements throughout Study M14-115.
9. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
10. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).
11. Subject who developed active Tuberculosis (TB) during Study M14-115, or subject who is non-compliant with prophylaxis for latent TB initiated per Study M14-115 procedures.

Investigational Products:	Adalimumab (40 mg/0.8 ml)
Doses:	**Open-Label Period** 40 mg eow or 40 mg ew for subjects whose disease is not controlled on 40 mg eow beginning at Week 0. No dose will be administered at Week 40.
Mode of Administration:	Subcutaneous (SC)

Duration of Treatment:

The study will include an open-label period of up to 40 weeks. There will be a 70-day follow-up phone call for subjects who complete the study or discontinue from the study prematurely. The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint

- Proportion of subjects with endoscopic improvement, defined as an SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment, at Week 40 among subjects with endoscopic improvement at Week 0 of Study M14-347.

Additional Efficacy Endpoints:

For additional efficacy endpoints, the baseline is defined as the Baseline in Study M14-115.

- Proportion of subjects with CDAI remission (CDAI < 150) at Week 40 among subjects with CDAI remission at Week 0 of Study M14-347.
- Proportion of subjects with a SFPS remission (SFPS < 50) at Week 40 among subjects with SFPS remission at Week 0 of Study M14-347.
- Proportion of subjects who achieve CDAI remission (CDAI < 150) over time.
- Time in CDAI remission (CDAI < 150) for subjects in CDAI remission at Week 0 of Study M14-347.
- Time to achieve CDAI remission (CDAI < 150) for subjects who were not in CDAI remission at Week 0 of Study M14-347.
- Time to first dose escalation.
- Proportion of subjects who require weekly dosing at Week 1 of Study M14-347.
- Time to achieve SFPS remission (SFPS < 50) for subjects who were not in SFPS remission at Week 0 of Study M14-347.
- Time in SFPS remission (SFPS < 50) among subjects with SFPS remission at Week 0 of Study M14-347.
- Proportion of subjects who achieve a Simplified Endoscopic Score for Crohn's Disease (SES-CD ≤ 4) with an Ulcerated Surface subscore no greater than 1 in any segment at Week 40.
- Proportion of subjects who achieve a SFPS < 50 over time.
- Proportion of subjects who entered Study M14-347 who were taking corticosteroids at Week 0 of Study M14-115 who discontinue corticosteroid use and achieved CDAI remission (CDAI < 150) at Week 40.
- Proportion of subjects who entered Study M14-347 who were taking corticosteroids at Week 0 of Study M14-115 who discontinue corticosteroid use at each visit.
- Proportion of subjects with CDAI response (decrease in CDAI ≥ 70 points from Baseline) over time.
- Proportion of subjects with enhanced CDAI response (decrease in CDAI ≥ 100 points from Baseline) over time.
- Proportion of subjects with endoscopic response (decrease ≥ 50% SES-CD from Baseline) at Week 40.
- Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Baseline) over time.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) over time.
- Change in IBDQ from Baseline over time.
- Change from Baseline in fecal calprotectin level over time.
- Change from Baseline in hs-CRP level over time.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional Efficacy Endpoints (Continued):

- Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 μg/g over time.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g over time.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment, and fecal calprotectin < 250 μg/g over time.
- Change in WPAI from Baseline over time.
- Change in European Quality of Life 5 Dimensions (EQ-5D) from Baseline over time.
- Change in CDAI from Baseline over time.
- Change in SFPS from Baseline over time.
- Change in Abdominal Pain Rating Scale score from Baseline over time.
- Proportion of subjects with major CD related event (e.g., hospitalization, bowel surgery, abscess drainage).
- Proportion of subjects with SES-CD = 0 at Week 40.
- Proportion of subjects with a decrease of SES-CD ≥ 3 points from Baseline of Study M14-115 at Week 40.
- Change in each CDAI component subscore (number of liquid or very soft stools, abdominal pain rating, general well-being, CD related complications, anti-diarrhea use, abdominal mass, hematocrit, body weight) from Baseline over time.
- Proportion of subjects requiring dose escalation to weekly dosing during this study.
- The proportion of subjects with no draining fistulas over time among subjects with draining fistula at Baseline of Study M14-115.
- The proportion of subjects in each treatment group with ≥ 50% reduction from Baseline of Study M14-115 in the number of draining fistulas over time among subjects with draining fistula at Baseline of Study M14-115.
- Proportion of subjects with CDAI < 150 at Week 40 and SES-CD ≤ 4 with an ulcerated surface subscore no greater than 1 in any segment at Week 40.
- Change in presence of extraintestinal manifestations over time.
- Proportion of subjects with predicted endoscopic improvement at Week 40, using the 3 definitions and equations listed below:
  1. Index score predicting the mucosal ulceration status (presence/absence) developed using retrospective CDEIS (≤ 4.24 versus > 4.24), laboratory and patient questionnaire data. The CDEIS based prediction index score is defined as

     $P_{CDEIS} = \exp(A)/[1+\exp(A)]$, where

     $A = 2.0291 - 0.0432*\text{Age} + 0.0429*\text{Albumin (g/L)} - 0.0060*\text{Platelet Count } (10^9/\text{L}) - 0.3286*\text{CRP (mg/dL)} - 0.0058*\text{CDAI1} - 0.001*\text{CDAI3}$
  2. Index score predicting the mucosal ulceration status (presence/absence) developed using retrospective visual assessment of ileocolonoscopy recordings, laboratory and patient questionnaire data. The visual assessment based prediction index score is defined as

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional Efficacy Endpoints (Continued):

P_{VISUAL} = exp(B)/[1+exp(B)], where

B = 1.142 – 0.013*Age – 0.061*Duration CD – 0.002*Platelet Count (10^9/L) – 0.138*CRP (mg/dL) – 0.228*Rectal Bleeding Previous Two Weeks – 0.01*CDAI1

3. Index score predicting the mucosal ulceration status (presence/absence) developed using retrospective SES-CD (≤ 5 versus > 5), laboratory and patient questionnaire data. The SES-CD based prediction index score is defined as

   P_{SESCD} = exp(C)/[1+exp(C)], where C = 1.796– 0.337 (If Female) – 0.002*Platelet Count (10^9/L) – 0.438*CRP (mg/dL) – 0.469*Rectal Bleeding Previous Two Weeks – 0.012*CDAI1 [CDAI1 and CDAI3 are Crohn's Disease Activity Index subscores 1 (liquid/soft stools) and 3 (general well-being) respectively.]

- Correlation between actual SES-CD and Predicted SES-CD (equation 2, above).
- Proportion of subjects who de-escalated the adalimumab dose from ew to eow in subjects who dose escalated.

Pharmacokinetic:

Blood samples for measurement of adalimumab concentrations will be obtained at Weeks 0 (from Week 12 of Study M14-115), 8, 16, 24, 32, 40/PD, and unscheduled visits if dose escalating or de-escalating. AAA concentrations will be obtained at Weeks 0, 24, 40/PD, and unscheduled visits if dose escalating or de-escalating.

Safety:

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.

Statistical Methods:

Efficacy:

The primary efficacy variable is proportion of subjects with CD with endoscopic improvement, defined as an SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment, at Week 40 among the subjects with endoscopic improvement at Week 0 of Study M14-347 A two-sided 95% confidence interval for the proportion will be calculated. The Intent-to-treat (ITT) set includes all subjects who enrolled into this study and received at least one dose of study drug. Missing SES-CD at Week 40 will be imputed using the non-responder imputation (NRI) approach. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses.

Statistical Methods (Continued):

Efficacy (Continued):

For categorical additional efficacy endpoints, the two-sided 95% confidence interval for the proportions will be provided. The non-responder imputation method will be used for subjects with missing data at the time point evaluated. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The LOCF method will also be used as the sensitivity analyses. For continuous additional efficacy endpoints, change from Baseline of Study M14-347 will be summarized by descriptive statistics using mean, standard deviation, minimum, median and maximum.

Both LOCF and observed case analyses will be performed.

For time to event additional efficacy endpoints, the number of event and the 25th, median, and 75th percentiles of time to event will be summarized.

Pharmacokinetic:

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

Immunogenicity:

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

Safety:

Laboratory data, AEs, and vital signs are the primary safety parameters in this study. All safety analyses will be performed using the Safety set, which includes all subjects who enrolled into this study and received at least one dose of study drug. Treatment emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 70 days after the last dose of the study drug. An overview of treatment-emergent AEs, including AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA Version 15.1 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Changes in laboratory data will be described using statistical characteristics. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-mercaptopurine
AAA	Anti-adalimumab antibody
ADA	Adalimumab
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-Reactive protein
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIM	Extra-Intestinal Manifestations
eow	every other week
ew	every week
EQ-5D	European Quality of Life 5 Dimensions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward

MedDRA	Medical Dictionary for Drug Regulatory Activities
MTX	Methotrexate
OLE	Open-Label Extension
PD	Premature Discontinuation
PK	Pharmacokinetics
RA	Rheumatoid arthritis
SAE	Serious adverse event
SC	Subcutaneous
SDP	Study designated physician
SES-CD	Simplified endoscopic score for Crohn's disease
SFPS	Stool [liquid/soft] Frequency + Abdominal Pain Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNF	Tumor Necrosis Factor
TB	Tuberculosis
UC	Ulcerative Colitis

2.0 Table of Contents

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3.0 Introduction

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

Traditionally, therapy for CD has been focused on symptomatic improvement and achievement of clinical remission as measured using the Crohn's disease activity index (CDAI). In addition to improving symptoms, an emerging goal of therapy is to improve the condition of the intestinal mucosa. It has been shown that patients with endoscopic evidence of ulceration of the gastrointestinal mucosa are at increased risk of experiencing a complicated disease course.[4] Therefore, it is reasonable that another goal of therapy be improvement of the intestinal mucosal as visualized on endoscopy; as this has been found to be associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries.[5,6] In addition, at the 2012 United States (US) Food and Drug Administration (FDA)-sponsored Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT) Workshop, there was significant discussion on the use of endoscopy to support determination of disease activity, as opposed to using symptomatic improvements alone. However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone as it requires reducing the extent of mucosal ulceration.

Study M14-115 assessed the efficacy and safety of two adalimumab induction regimens in achieving endoscopic improvement, (SES-CD $\leq$ 4 with an Ulcerated Surface sub-score no

greater than 1 in any segment) at Week 12 and clinical remission (CDAI < 150) at Week 4 as well as the pharmacokinetics (PK) and immunogenicity of the two adalimumab induction regimens. This study is designed to investigate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in adult subjects with CD who participated and successfully completed Study M14-115.

3.1 Differences Statement

Study M14-347 is a Phase 3 open-label clinical study to evaluate the long-term efficacy, safety, and tolerability of adalimumab in the treatment of adult subjects with CD who participated in and successfully completed Study M14-115. Subjects will receive adalimumab 40 mg every other week (eow) with the opportunity to dose escalate to adalimumab 40 mg every week (ew), if the subject meets the criteria for inadequate response as defined in Table 1.

3.2 Benefits and Risks

Extensive clinical and post marketing experience exists with adalimumab in a wide range of disease states including CD and ulcerative colitis (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 CD have not altered this safety profile and demonstrated a positive benefit/risk balance. Conditions which may present a risk specifically for patients with CD are exclusion criteria in this study (e.g., evidence of colonic dysplasia or active infections).

3.3 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1,330 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 tumor necrosis factor (TNF), and human IgG1

heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

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

Adalimumab was first approved in US and EU for the treatment of rheumatoid arthritis (RA) in 2002 and 2003, respectively. Additional indications have been approved in the US and EU including psoriasis, psoriatic arthritis, axial spondylitis, CD, juvenile arthritis and UC. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

3.4 Safety information

Adalimumab therapy has a well-established and well described safety profile in adults based on extensive post marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for RA. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in a FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in patients who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional

reporting requirements needed in this unlikely event, outlined in Section 6.5 under Adverse Event Reporting.

4.0 Study Objectives

The primary objective of this study is to evaluate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in subjects with CD who participated in and successfully completed Study M14-115.

The secondary objective is to assess PK and immunogenicity of adalimumab following subcutaneous (SC) administration.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, multicenter, open-label extension (OLE) study which comprises a 40-week open-label period designed to evaluate the long-term efficacy, safety, and tolerability of adalimumab. Approximately 300 adult subjects who participated and successfully completed Study M14-115 and who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to enroll into this study.

Subjects will be evaluated for entry into Study M14-347 at the final study visit (Week 12) of Study M14-115. A subject's participation in the study is anticipated to be up to 40 weeks. There is a ± 3-day window for all study visits. An effort will be made to bring the subject back to their original study visit (calculated from Week 0) if they are out of the visit window.

Study visits for clinical and safety assessments will be performed at Weeks 0, 8, 16, 24, 32 and 40/Premature Discontinuation (PD). All subjects will be provided with a paper subject diary in which they will record CD-related symptoms (number of liquid or very soft stools, abdominal pain rating, general well-being) and adalimumab dosing information throughout the study. Blood samples will be collected at various time points for routine labs, along with hs-CRP, adalimumab serum concentrations, anti-adalimumab

antibody (AAA) levels and other biomarker analyses. In addition, stool samples for calprotectin and microbiota will be collected. The stool samples should be taken before starting bowel preparations for endoscopy. Endoscopic evaluation will be performed at Week 40/PD, if the PD occurs after Week 24. CDAI evaluations will be calculated based on entries recorded into the subject's diary at all study visits. The SFPS (Stool [liquid/soft] Frequency + Abdominal Pain Score) will be calculated using the weighted values for the CDAI components "Number of liquid or very soft stools" and "Abdominal pain."

The Week 12 visit of Study M14-115 will be considered Week 0 (Baseline) of Study M14-347. All subjects will receive open-label adalimumab 40 mg every other week (eow) beginning at Week 0. No dose will be administered at Week 40. Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 1 should the subject meet the criteria for inadequate response (Table 1).

Table 1. Inadequate Response

Response Type	Definition
Inadequate response	Crohn's disease activity index (CDAI) of ≥ 200 at any one visit and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L. The hs-CRP results used to determine inadequate response can be from the prior or current visit. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.

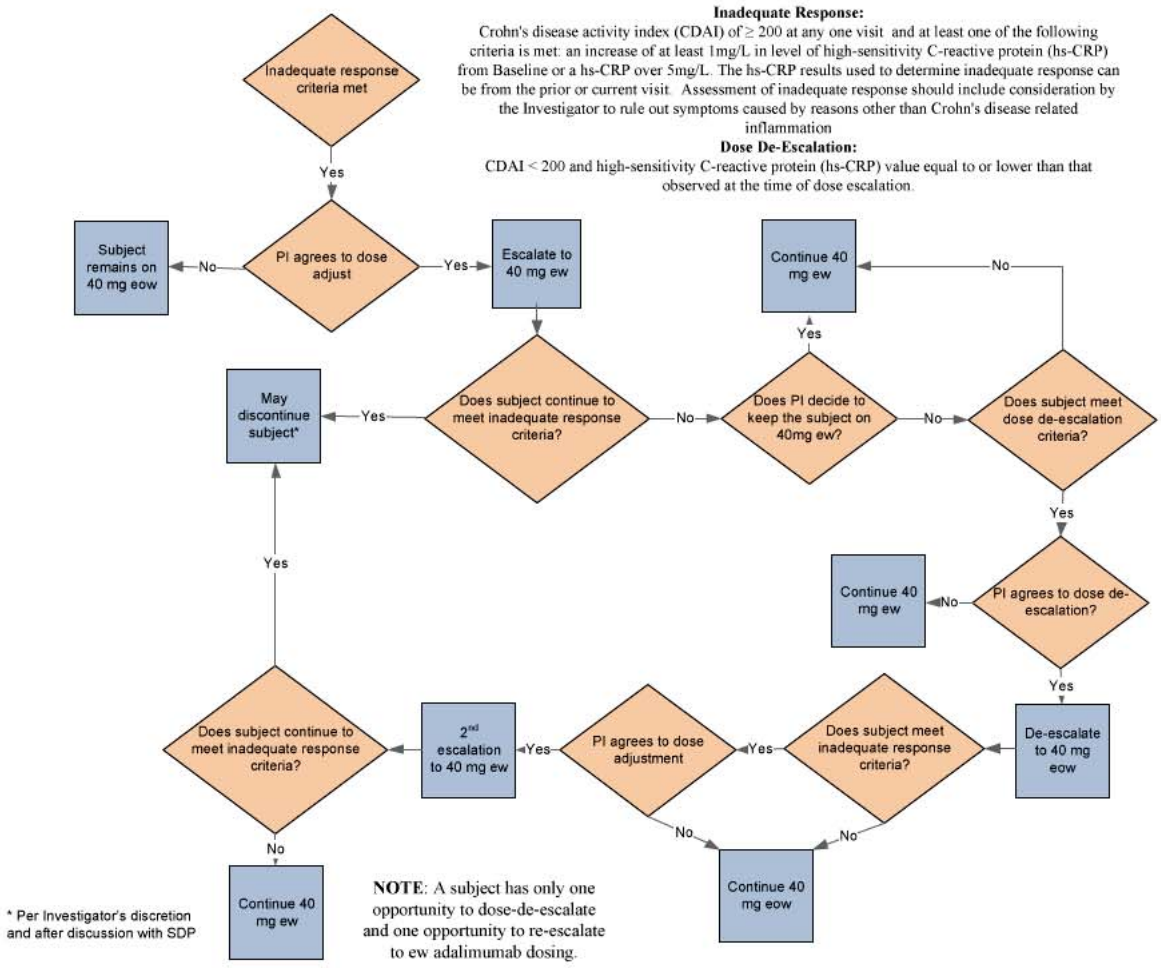
For subjects taking corticosteroids at Baseline of Study M14-115 adalimumab dose escalation should be considered in lieu of increases in steroid dose. Subjects who continue to experience inadequate response on 40 mg ew who were taking corticosteroids at Baseline of Study M14-115 may have their steroid dose increased, per the Investigator's discretion, in order to manage the subject's symptoms. Any subject who continues to experience inadequate response on 40 mg ew may be discontinued from the study at the investigator's discretion after discussion with the study designated physician (SDP). Subjects who dose escalated to adalimumab 40 mg ew, have **one** opportunity to de-

escalate adalimumab dose to 40 mg eow provided the following criteria have been met: CDAI < 200 and high-sensitivity C-reactive protein (hs-CRP) value equal to or lower than that observed at the time of dose escalation. Subjects who experience inadequate response after dose de-escalation (using the same criteria outlined above), may again be escalated to 40 mg ew. A subject has only **one** opportunity to dose de-escalate and one opportunity to re-escalate to ew adalimumab dosing.

Changes in adalimumab dosing may only occur when the above criteria are met but are not mandatory.

A schematic for dose adjustments is presented in Figure 1.

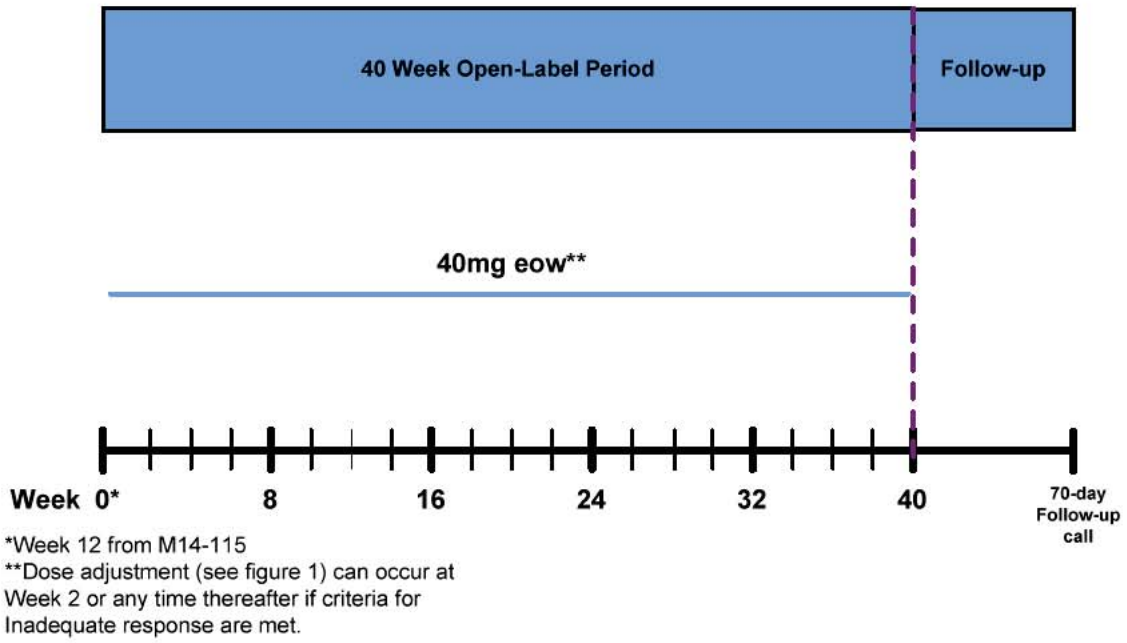
Figure 1. Dose Adjustment Algorithm



Subjects may discontinue adalimumab treatment at any time during study participation (Section 5.4). Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator. Subjects who end study participation early will have a PD visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs). The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

A schematic of the study design is presented in Figure 2.

Figure 2. Study Schematic



Clinical evaluation will be completed at each study visit. See activities outlined in Table 2.

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

- Immunosuppressant doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.
- Subjects who are taking corticosteroid therapy at Baseline of Study M14-115 should continue the steroid taper initiated during Study M14-115. Increases in steroid doses back to the dose used at Baseline of Study M14-115 to manage inadequately controlled CD-related symptoms may be undertaken at the Investigator's discretion in subjects who are receiving adalimumab 40 mg ew. For subjects taking adalimumab 40 mg eow, adalimumab dose escalation

(for subjects who meet inadequate response criteria) should be considered in lieu of increases in the steroid dose.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Subject must have successfully enrolled in and completed Study M14-115, including the Week 12 ileocolonoscopy.
2. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently are (see local informed consent for more detail):
   - Implants, injectables, some intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS)
   - Sexual abstinence (when in line with preferred and usual lifestyle of the subject)
   - Vasectomized partner
   - Hormonal contraceptives for at least 90 days prior to study drug administration

     Note: low-dose progestin-only oral contraceptives such as norethindrone 0.35 mg and lynestenol 0.5 mg are not considered adequate
3. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
4. Subject must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.

Criteria	Rationale
1 – 4	In order to select the appropriate subject population with a disease status representative of the target population for evaluation.

5.2.2 Exclusion Criteria

1. For any reason subject is considered by the investigator to be an unsuitable candidate.
2. Known hypersensitivity to adalimumab or its excipients.
3. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
4. Positive pregnancy test at Baseline (Week 12 of Study M14-115).
5. Female subject who is considering becoming pregnant during the study.
6. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma and/or localized carcinoma in situ of the cervix. If the Week 12 (Study M14-115) colonoscopy shows evidence of dysplasia or a malignancy, subject must not be enrolled in the study.
7. Subject with a poorly controlled medical condition, such as uncontrolled diabetes, unstable ischemic heart disease, moderate or severe congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the investigator or sponsor, would put the subject at risk by participation in this study.
8. Subject is not in compliance with prior and concomitant medication requirements throughout Study M14-115.
9. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
10. History of invasive infection (e.g., listeriosis and histoplasmosis) or human immunodeficiency syndrome (HIV).

11. Subject who developed active Tuberculosis (TB) during Study M14-115, or subject who is non-compliant with prophylaxis for latent TB initiated per Study M14-115 procedures.

Criteria	Rationale
1 – 7, 9 – 11	To reduce the risk to subjects or others and/or to exclude underlying conditions that would compromise the subject's safety.
8	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications or treatments.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior Therapy

Subjects may continue taking permitted therapies from Study M14-115.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment into M14-347, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF).

The AbbVie SDP identified in Section 6.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

In addition, for subjects age ≤ 30 with a reported malignancy AE, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate electronic case report form (eCRF) pages. At the time of the reported malignancy AE, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use,

date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

5.2.3.2 Concomitant Therapy

Doses of immunosuppressants (including but not limited to) azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), aminosalicylates, and CD-related medications taken at Baseline of Study M14-347 will be continued. Doses must remain stable throughout the duration of the study. Doses may be decreased or terminated, in the event of treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the investigator, or, in the case of CD-related antibiotics, concerns about antibiotic resistance.

Subjects in whom systemic corticosteroids that were not being taken at Baseline of Study M14-347 and are initiated during the study or who have dosages of corticosteroids increased to greater than the dose taken at Baseline of Study M14-115 may continue in the study, but will be censored for efficacy assessments (i.e., will be considered non-responders for categorical endpoints and will have Baseline values (from Study M14-115) carried forward for non-categorical assessments) from that point through the end of the study. These subjects will continue to be evaluated in the safety population.

Subjects who enter the study on probiotics may continue this therapy provided doses remained stable during Study M14-115 and remain stable during the duration of Study M14-347.

The AbbVie SDP identified in Section 6.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following:
  - Etanercept (Enbrel®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Efalizumab (Raptiva®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);
  - Infiximab (Remicade®);
  - Certolizumab pegol (Cimzia®);
  - Golimumab (Simponi®);
  - Vedolizumab (Entyvio®).
- Tofacitinib (Xeljanz®)
- NSAIDs (excluding topical)
- Live vaccines (during the study and for 70 days after the last dose of study drug)
- Cyclosporine, tacrolimus, or mycophenolate mofetil
- Recreational or medical marijuana use

Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy, is prohibited during the study.

Intravenous corticosteroid use is prohibited during the study.

Investigational drugs of a chemical or biologic nature are prohibited during the study.

The AbbVie SDP identified in Section 6.5 should be contacted if there are any questions regarding prohibited therapy.

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in Table 2 and Section 5.3.1.1. All l subjects must meet the study selection criteria outlined in Section 5.2.1 and Section 5.2.2.

Table 2. Study Activities

Activity	Baseline (Week 0)[a]	Week 8	Week 16	Week 24	Week 32	Week 40/ Premature Discontinuation	Unscheduled Visit[k]	70-Day Follow-Up Call[l]
Informed Consent	X							
Inclusion/Exclusion[b]	X							
Medical/Surgery History Update[b]	X							
Previous and Concomitant Medication Update[b]	X	X	X	X	X	X	X	
Vital Signs	X[a]	X	X	X	X	X	X	
Endoscopy[c]	X[a]					X		
SES-CD Score	X[a]					X		
Physical Examination[d]	X[a]	X	X	X	X	X	X	
Urinalysis[e]	X[a]	X	X	X	X	X	X	
Pregnancy Tests[f]	X[a]					X		
Chemistry and Hematology[h]	X[a]	X	X	X	X	X	X	
hs-CRP	X[a]	X	X	X	X	X	X	
Provide Stool Kit[g]	X	X	X	X	X		X	
Stool Sample (fecal calprotectin)[g]	X[a]	X	X	X	X	X	X	
Stool Sample (microbiota metagenomic analyses)[g]	X[a]			X		X		
Bristol Stool Scale for Metagenomic Analysis[g]	X[a]			X		X		
Adalimumab Concentration[h]	X[a]	X	X	X	X	X	X	
AAA Concentration[h]	X[a]			X		X	X	
Serological Biomarkers/mRNA	X[a]			X		X		

Table 2. Study Activities (Continued)

Activity	Baseline (Week 0)[a]	Week 8	Week 16	Week 24	Week 32	Week 40/ Premature Discontinuation	Unscheduled Visit[k]	70-Day Follow-Up Call[l]
Crohn's Disease Activity Index (CDAI)	X[a]	X	X	X	X	X	X	
Inflammatory Bowel disease Questionnaire (IBDQ)	X[a]		X		X	X		
European Quality of Life 5 dimensions (EQ-5D)	X[a]		X		X	X		
Work Productivity and Impairment Questionnaire (WPAI)	X[a]		X		X	X		
Abdominal Pain Rating Scale	X[a]		X		X	X		
Monitor Adverse Events[i]	X[a]	X	X	X	X	X	X	X
Study Drug Dispensing/Administration[j]	X	X	X	X	X			
Subject Diary Review	X[m]	X	X	X	X	X	X	

a. Information from the activities completed at Week 12 of Study M14-115 will be carried over to the Baseline visit and will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits.

b. Inclusion/exclusion, prior and concomitant therapy, and medical/surgical history information will be assessed to assure subject eligibility.

c. An ileocolonoscopy will be performed at Week 40/PD, if the PD occurs after Week 24. A biopsy will be performed at Week 40/PD if a suspicious lesion or suspected malignancy, in the assessment of the Investigator, is observed, and evaluated by the local pathologist. Biopsies to evaluate suspicious lesions and to rule out malignancy may be taken during any study endoscopy per the Investigator's discretion and evaluated by the local pathologist.

d. Physical examination performed at Week 40/Premature Discontinuation Visit is a full physical examination which must include an assessment of extra-intestinal manifestations (EIMs) and a count of the number of cutaneous fistulas. Physical examinations performed at all other visits are symptom based and must include a count of the number of cutaneous fistulas.

e. 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.

Table 2. Study Activities (Continued)

f. Urine pregnancy test results from Week 12 of Study M14-115 will be carried over to the Baseline Visit. Urine pregnancy test will be performed at Week 40/PD for all women of childbearing potential. The frequency can be increased up to every visit as per local regulations. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

g. A stool sample will be collected for fecal calprotectin and metagenomic analysis at each time points indicated. Subjects will be sent home with instructions and a stool sample supply kit (supplies will be provided at the time points indicated). The stool from which these samples are prepared should be scored using the Bristol stool scale by site. Stool samples for metagenomic analysis should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection.

h. Blood samples for the measurement of adalimumab and anti-adalimumab antibody (AAA) concentrations will be collected prior to dosing. If the subject is dose escalating or de-escalating, blood samples will be taken prior to dosing for the measurement of adalimumab and AAA concentrations which may occur at an unscheduled visit.

i. Collection of serious adverse events (SAEs) begins the day the subject signs the informed consent.

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

k. Visits for dispensing new study drug in case of temperature excursion, loss, damage, or dose escalation are not considered an Unscheduled Visit. In addition, visits to retest a lab will not be considered an Unscheduled Visit. Unscheduled visits can be used for situations including the following: For evaluation and assessment of the subject, to evaluate a subject who meets criteria for inadequate response as outlined in Table 1, to collect samples to determine hs-CRP in those subjects, and to collect PK samples for a change in adalimumab dosing.

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

m. Sites will review the electronic diary utilized and collected from Week 12 of Study M14-115 to obtain the number of liquid or very soft stools, abdominal pain rating, general well-being and adalimumab dosing information. A new paper subject diary will be dispensed to subjects at Baseline. 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 Final/PD visit.

5.3.1.1 Study Procedures

The study procedures outlined in Table 2 are discussed in detail in this section, with the exception of drug concentration measurements, antibody measurements, serological and mRNA biomarkers (discussed in Section 5.3.1.2 and Section 5.3.6), and the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

At the Baseline visit (Week 12 of Study M14-115), the subject will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Details regarding how informed consent will be obtained and documented are provided in Section 9.3. Consent will be required for any optional testing.

Inclusion/Exclusion Criteria

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

Medical and Surgical History

An update to the medical and surgical history from Study M14-115 will be obtained from each subject during 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.

Endoscopy

An endoscopy will be performed on the following visits:

- Week 12 of Study M14-115 for Baseline measure
- Week 40/Premature Discontinuation if PD occurs after Week 24

An ileocolonoscopy will be performed and should be recorded at the site in a video format. Sites should also perform an SES-CD assessment and record findings on the provided SES-CD score sheet, refer to Appendix K. The findings should be entered in the appropriate eCRF. Two primary central reviewers will evaluate the data and provide their score. A third central reviewer will re-read (adjudicate) the endoscopy if there is a discrepancy between the two primary central reviewers. The adjudicator's assessment will be considered final.

The endoscopy at Week 40/PD will be used to provide the endoscopy subscores for calculating the Simplified endoscopic score for Crohn's disease (SES-CD) at Week 40/PD, refer to Appendix K. The SES-CD values provided by the central reader will be used for all endpoint analyses. The same endoscopist, where possible, should perform all endoscopies.

Biopsy During Endoscopy

During the Week 40/PD endoscopy, biopsies to evaluate suspicious lesions or to rule out malignancy may be taken per the Investigator's discretion and evaluated by the local pathologist. If a biopsy sample is obtained, the sampling should be recorded and the sampling should not interfere with the recording the central reviewers will use for their evaluation. The signed pathology report will be monitored by the responsible Clinical Research Associate (CRA) and kept with the subject's source documents onsite. Subjects should not be enrolled if colon dysplasia or malignancy is discovered at the Study M14-115 Week 12 endoscopy. If colon dysplasia or malignancy is discovered during any subsequent endoscopic evaluation during the course of the study, the findings should be recorded as an AE and the subject should be discontinued from the study.

Physical Examination

A full physical examination will be performed and must include an assessment of extra-intestinal manifestations (EIMs) and a count of the number of cutaneous fistulas at visits indicated in Table 2. The physical examination at Week 12 of Study M14-115 will serve as the Baseline physical examination for the entire study. Symptom-based examinations will be performed at all other visits; however, a count of the number of cutaneous fistulas draining upon gentle compression will be performed during each physical exam. Fistulas will be classified as abdominal or perianal/anal. Physical exam abnormalities noted by the investigator at Week 12 from Study M14-115 (including fistulas and fissures) will be recorded in the subject's medical history.

Abnormalities noted after the Baseline visit will be evaluated and documented by the investigator as to whether they are AEs.

Additional physical examination findings that are related to or part of each subject's medical history will be captured on the appropriate medical history CRFs.

Urinalysis

Urine samples will be obtained and sent to the central laboratory for the tests listed in Table 3. Microscopic urinalysis will only be performed by the central laboratory if the dipstick UA results are abnormal, where abnormal is defined as a protein, ketones or blood greater than negative or glucose greater than normal.

Pregnancy Tests

Subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel at the time points indicated in Table 2. The frequency can be increased up to every visit as per local regulations. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Clinical Laboratory Tests

Blood samples will be obtained for the laboratory tests listed in Table 3. Blood draws should be performed after efficacy assessments and questionnaires (CDAI, IBDQ, etc.), vital sign determinations are obtained and before study drug administration during a visit.

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

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

Table 3. 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 Serum glutamic-pyruvic transaminase/Alanine transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase/Aspartate transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity Ketones pH Protein Blood Glucose **Stool Samples Collected** Fecal calprotectin Microbiota metagenomic analyses
Additional Blood Samples Collected		
hs-CRP Pharmacokinetic mRNA Serologic Biomarkers		

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

hs-CRP

Blood samples for hs-CRP will be obtained per Table 2.

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

Other Laboratory Assessments

Stool Sample (Fecal Calprotectin and Microbiota Metagenomic Analyses)

Fecal calprotectin and microbiota metagenomic analysis will be performed for all subjects as indicated in Table 2. Subjects will be sent home with a stool sample supply kit and instructions at the prior visit. The fecal calprotectin sample will also be collected prior to dose escalation or dose de-escalation.

All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection. All microbiota metagenomic analyses stool samples should be scored by site staff using the Bristol stool scale (Appendix L). The score of the Bristol stool scale at Baseline in this study will be scored using the electronic diary from Study M14-115. A central laboratory(s) will be utilized to process these laboratory tests.

Where allowed by local guidelines at the time of stool collection any remaining stool could be used for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or development of AEs. These samples may also be used for the development of diagnostic tests. Results of exploratory analyses, if any, will not be reported with the study summary. AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for no longer than 20 years after completion of the study (where allowed by local guidelines) for possible future research.

Crohn's Disease Activity Index (CDAI)

A CDAI score will be calculated from a subject diary, physical exam, and appropriate laboratory values at all study visits beginning at Baseline. The CDAI calculated at Week 12 in Study M14-115 will serve as the Baseline CDAI for this open-label extension study.

Beginning with the Week 0 through Week 40 visits, including unscheduled visits, the CDAI scores must be calculated using a hematocrit value from the preceding visit laboratory work.

CDAI at Visit	HCT Value Utilized
Week 0	Week 8 (Study M14-115)
Week 8	Week 0
Week 16	Week 8
Week 24	Week 16
Week 32	Week 24
Week 40	Week 32

For calculation of CDAI scores used to determine if subjects meet the criteria for inadequate response, the hematocrit value used to calculate the first CDAI score can also be used to calculate the second CDAI score.

For calculating CDAI at Week 0 thru Week 40/PD, to answer questions one (1) through three (3), entries from the 7 days prior to the visit should be used as recorded by the subject from the diary. Diary entries for calculating CDAI should not be included in the 7 days evaluated prior to the visit if: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 7 days prior to the respective study visit.

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

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

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

The height obtained from Study M14-115 should be used when selecting the standard weight in Appendix I, and this standard weight should be used for calculating every CDAI throughout subject participation in the study.

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

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

The calculation of the CDAI score is in Appendix H.

Patient Reported Outcomes and Questionnaires

- IBDQ – Inflammatory Bowel disease Questionnaire (IBDQ) will be completed at the time points indicated in Table 2 (Appendix E).
- WPAI – Work Productivity and impairment Questionnaire will be completed at the time points indicated in Table 2. The data in the subject-completed questionnaire will be transferred to the appropriate eCRF by the site personnel at each study visit (Appendix C).
- EQ-5D – A standardized questionnaire for use as a measure of health outcome (Appendix D).
- Abdominal pain rating scale (Appendix F).

Study Drug Dispensing/Administration

Study drug will be administered to all subjects onsite by either site medical staff or the subjects or designee (friend, family member or health care professional) during the first visit. Detailed instructions and training for the administration of adalimumab are provided in Appendix G.

Adalimumab injections occurring during study visits will be performed at the visit by the subject or their designated family member, friend or Healthcare Professional under the supervision of trained medical personnel to reinforce proper aseptic SC injection technique. Subjects or a trained designated family member, friend or Healthcare Professional will perform the injections of adalimumab in the subject's home during the weeks they are not in for scheduled clinic visits.

Subjects should administer study drug 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 who deviate from this dosing window, every effort should be made to bring the subject back to the original dosing schedule as soon as possible. For situations where bringing the subject back on the original dosing schedule will cause the dose to be out of the ± 3-day window, please contact the AbbVie SDP for additional instructions.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study drug should be discontinued immediately and initiate appropriate therapy. When dosing at home subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction. If subjects are unable to reach their study site or experience life-threatening symptoms, they will be instructed to call an emergency number or proceed to the nearest emergency room and then inform the site as soon as possible.

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

Subject Diary

The subject's electronic diary will be reviewed and collected from Week 12 of Study M14-115 to obtain the number of liquid or very soft stools, abdominal pain rating, general well-being, use of medications used for endoscopy preparation, and adalimumab dosing information. A new paper subject diary will be dispensed to subjects at Baseline. All subjects should complete their subject diary on a daily basis throughout the entire study. The diary will be reviewed by site personnel with the subject at each visit and collected at the Final/PD visit.

The dosing records will be reviewed and verified for compliance at each visit by the research personnel at the study center and reinforced if necessary. 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.

5.3.1.2 Blood Samples for Biomarkers Analysis

Collection of Samples for Serologic Markers

Two 5 mL blood samples for serologic markers analysis will be collected at the time points indicated in Table 2. Please refer to the laboratory manual for specific instructions. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

The frozen serum and plasma samples for serologic marker analysis will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. An inventory of the samples included will accompany the package. Arrangements will be made with the central laboratory for the shipment of samples to AbbVie or specified lab for testing.

See Section 5.3.6 for the variables of this analysis.

Collection of Samples for mRNA Assays

Two 2.5 mL blood samples for mRNA will be collected at the time points indicated in Table 2. Please refer to the laboratory manual for specific instructions.

The frozen samples for mRNA analysis will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory. Samples should not be allowed to thaw prior to arrival at AbbVie or the designated laboratory. An inventory of the samples included will accompany the package. Arrangements will be made with the central laboratory for the shipment of samples to AbbVie or specified lab for testing.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for adalimumab and AAA concentrations will be obtained at the time points as indicated in Table 2. Some samples might be obtained and stored to analyze for factors contributing to the subject's response to study treatment, in terms of pharmacokinetics, pharmacodynamics, tolerability or safety after the study.

The time that each blood sample is collected will be recorded to the nearest minute in the source document and on the appropriate eCRF.

Collection of Samples for Adalimumab and AAA Assays

Blood samples for adalimumab and AAA assays will be collected by venipuncture into appropriately labeled 4-mL evacuated serum collection tubes (one tube for adalimumab and one tube for AAA) without gel separator immediately prior to dosing. Sufficient blood will be collected to provide approximately 2 mL serum for adalimumab assay and 2 mL serum for AAA assay. Please refer to the laboratory manual for instructions.

For subjects who meet the criteria for a dose adjustment (escalation or de-escalation), blood samples for the measurement of serum adalimumab and AAA concentrations will be collected just prior to receiving their first adjusted dose of adalimumab.

A maximum number of samples that a subject could have collected over the duration of the study would be 7 blood samples (not including unscheduled visit sample collections): 5 samples for the determination of adalimumab concentrations, and 2 samples for the determination of AAA concentrations. The total number of samples will not exceed 1,500 (5 samples × 300 subjects) for the adalimumab assay and 600 (2 samples × 300 subjects) for the AAA assay for the entire study.

5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA concentrations will be labeled with information such as the following: the type of sample, the study drug number, protocol number, subject number, study week/visit name, and assay type (PK-Adalimumab or AAA).

Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory.

5.3.2.3 Disposition of Samples

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

5.3.2.4 Measurement Methods

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

5.3.3 Efficacy Variables

Term	Definition
Endoscopic Improvement	SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment
CDAI Remission	CDAI < 150
SFPS Remission	SFPS < 50
Response per CDAI	A reduction in CDAI by ≥ 70 (CR-70) from baseline*
Enhanced response per CDAI	Decrease in CDAI ≥ 100 (CR-100) from baseline*
Endoscopic response	Decrease ≥ 50% SES-CD from Baseline
IBDQ Response	Increase in IBDQ score ≥ 16 point from Baseline*
IBDQ Remission	IBDQ ≥ 170

* Baseline in the additional efficacy variables is defined as the Baseline in Study M14-115.

5.3.3.1 Primary Efficacy Variables

Proportion of subjects with endoscopic improvement, defined as an SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment, at Week 40 among subjects with endoscopic improvement at Week 0 of Study M14-347.

5.3.3.2 Additional Efficacy Variables

For additional efficacy endpoints, the baseline is defined as the Baseline in Study M14-115.

- Proportion of subjects with CDAI remission (CDAI < 150) at Week 40 among subjects with CDAI remission at Week 0 of Study M14-347.
- Proportion of subjects with a SFPS remission (SFPS < 50) at Week 40 among subjects with SFPS remission at Week 0 of Study M14-347.
- Proportion of subjects who achieve CDAI remission (CDAI < 150) over time.
- Time in CDAI remission (CDAI < 150) for subjects in CDAI remission at Week 0 of Study M14-347.
- Time to achieve CDAI remission (CDAI < 150) for subjects who were not in CDAI remission at Week 0 of Study M14-347.
- Time to first dose escalation.

- Proportion of subjects who require weekly dosing at Week 1 of Study M14-347.
- Time to achieve SFPS remission (SFPS < 50) for subjects who were not in SFPS remission at Week 0 of Study M14-347.
- Time in SFPS remission (SFPS < 50) among subjects with SFPS remission at Week 0 of Study M14-347.
- Proportion of subjects who achieve a Simplified Endoscopic Score for Crohn's Disease (SES-CD ≤ 4) with an Ulcerated Surface subscore no greater than 1 in any segment at Week 40.
- Proportion of subjects who achieve a SFPS < 50 over time.
- Proportion of subjects who entered Study M14-347 who were taking corticosteroids at Week 0 of Study M14-115 who discontinue corticosteroid use and achieved CDAI remission (CDAI < 150) at Week 40.
- Proportion of subjects who entered Study M14-347 who were taking corticosteroids at Week 0 of Study M14-115 who discontinue corticosteroid use at each visit.
- Proportion of subjects with CDAI response (decrease in CDAI ≥ 70 points from Baseline) over time.
- Proportion of subjects with enhanced CDAI response (decrease in CDAI ≥ 100 points from Baseline) over time.
- Proportion of subjects with endoscopic response (decrease ≥ 50% SES-CD from Baseline) at Week 40.
- Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Baseline) over time.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) over time.
- Change in IBDQ from Baseline over time.
- Change from Baseline in fecal calprotectin level over time.
- Change from Baseline in hs-CRP level over time.
- Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g over time.

- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g over time.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment, and fecal calprotectin < 250 μg/g over time.
- Change in WPAI from Baseline over time.
- Change in European Quality of Life 5 Dimensions (EQ-5D) from Baseline over time.
- Change in CDAI from Baseline over time.
- Change in SFPS from Baseline over time.
- Change in Abdominal Pain Rating Scale score from Baseline over time.
- Proportion of subjects with major CD related event (e.g., hospitalization, bowel surgery, abscess drainage).
- Proportion of subjects with SES-CD = 0 at Week 40.
- Proportion of subjects with a decrease of SES-CD ≥ 3 points from Baseline of Study M14-115 at Week 40.
- Change in each CDAI component subscore (number of liquid or very soft stools, abdominal pain rating, general well-being, CD related complications, anti-diarrhea use, abdominal mass, hematocrit, body weight) from Baseline over time.
- Proportion of subjects requiring dose escalation to weekly dosing during this study.
- The proportion of subjects with no draining fistulas over time among subjects with draining fistula at Baseline of Study M14-115.
- The proportion of subjects in each treatment group with ≥ 50% reduction from Baseline of Study M14-115 in the number of draining fistulas over time among subjects with draining fistula at Baseline of Study M14-115.
- Proportion of subjects with CDAI < 150 at Week 40 and SES-CD ≤ 4 with an ulcerated surface subscore no greater than 1 in any segment at Week 40.
- Change in presence of extraintestinal manifestations over time.

- Proportion of subjects with predicted endoscopic improvement at Week 40, using the 3 definitions and equations listed below:

1. Index score predicting the mucosal ulceration status (presence/absence) developed using retrospective CDEIS (≤ 4.24 versus > 4.24), laboratory and patient questionnaire data. The CDEIS based prediction index score is defined as

   $P_{CDEIS} = \exp(A)/[1+\exp(A)]$, where

   A = 2.0291 – 0.0432*Age + 0.0429*Albumin (g/L) – 0.0060*Platelet Count (10^9/L) – 0.3286*CRP (mg/dL) – 0.0058*CDAI1 – 0.001*CDAI3,

2. Index score predicting the mucosal ulceration status (presence/absence) developed using retrospective visual assessment of ileocolonoscopy recordings, laboratory and patient questionnaire data. The visual assessment based prediction index score is defined as

   $P_{VISUAL} = \exp(B)/[1+\exp(B)]$, where

   B = 1.142 – 0.013*Age – 0.061*Duration CD – 0.002*Platelet Count (10^9/L) –

   – 0.138*CRP (mg/dL) – 0.228*Rectal Bleeding Previous Two Weeks –

   – 0.01*CDAI1

3. Index score predicting the mucosal ulceration status (presence/absence) developed using retrospective SES-CD (≤ 5 versus > 5), laboratory and patient questionnaire data. The SES-CD based prediction index score is defined as

   $P_{SESCD} = \exp(C)/[1+\exp(C)]$, where

   C = 1.796– 0.337 (If Female) – 0.002*Platelet Count (10^9/L) – 0.438*CRP (mg/dL)

   – 0.469*Rectal Bleeding Previous Two Weeks – 0.012*CDAI1

[CDAI1 and CDAI3 are Crohn's Disease Activity Index subscores 1 (liquid/soft stools) and 3 (general wellbeing) respectively.]

- Correlation between actual SES-CD and Predicted SES-CD (equation 2, above).
- Proportion of subjects who de-escalated the adalimumab dose from ew to eow in subjects who dose escalated.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

Blood samples will be collected for measurement of serum adalimumab concentration just prior to dosing and AAA outlined in Table 2.

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

5.3.6 Serologic Variables

Samples may be analyzed for plasma and serum proteins, peptides, and non-protein soluble factors such as lipids that may help predict disease behavior and help determine more severe disease phenotypes.

Where allowed by local guidelines at the time of the blood draw for biomarkers, serum may be stored for possible future research. Samples will be stored frozen for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or development of AEs. These samples

may also be used for the development of diagnostic tests. Results of exploratory analyses, if any, will not be reported with the study summary. AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. As allowed by local guidelines, the samples will be retained for up to 20 years after completion of the study research.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an AE, 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 AE(s), as determined by the Investigator in consultation with the AbbVie SDP.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study would place the subject at risk as determined by the AbbVie SDP (Section 5.2.1 and Section 5.2.2).
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie SDP.
- The subject becomes pregnant while on study drug.
- Subject has dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.

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

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

A final phone call will be made to the subject approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up phone call will not be required for any subject who initiates commercial adalimumab.

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

5.4.2 Discontinuation of Entire Study

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

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

5.5 Treatments

5.5.1 Treatments Administered

All subjects will receive open-label adalimumab 40 mg eow or ew at Week 0 (Week 12 of Study M14-115) until Week 38 (Week 39 for subjects receiving weekly dosing). No drug will be administered at Week 40. Subjects can also escalate and de-escalate adalimumab treatment as described in Section 5.1.

5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 4.

Table 4. Study Drugs

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Pre-filled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie

5.5.2.1 Packaging and Labeling

Investigational product will be provided in a kit that contains 2 pre-filled syringes containing adalimumab 40 mg/0.8 mL injection solution. Each dosing kit carton contains pre-filled syringes to accommodate study design. The syringe and/or carton labels will minimally contain the information as required per country requirements.

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

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

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study drug ***must not be frozen at any time***. A storage temperature log is to be maintained to document proper storage conditions. The clinical site refrigerator temperature must be recorded on a temperature log to record proper function.

Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study drug should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) deems the study drug 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.

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

All subjects will be centrally registered using an Interactive Voice Response System (IVRS). There will be no randomization for this open-label study. Subjects will keep their study subject number from the previous Study M14-115. Before the study is initiated, the directions for the IVRS will be provided to each site. Returned study drug should not be re-dispensed to any subject.

Study drug will be administered at the study visits summarized in Table 2.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in Section 5.1.

If a subject should forget to administer the injection of study drug 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 in the Subject Diary.

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

5.5.5 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study.

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 diary to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of study drug. If the subject does not return the diary, IP boxes and sharps containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

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

5.5.6 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the site on a Site Drug Accountability log including date received, the lot number, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug. For this study, unless otherwise prohibited locally, these records will be maintained electronically as part of the IVRS/IWRS system.

All empty IP boxes and used pre-filled syringes will be inventoried by the site. Each subject will be given their own sharps disposal container to store used pre-filled syringes. Empty IP boxes and sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty boxes and returned sharps containers will be retained (unless prohibited by local law) until the CRA is on site to confirm the returned study drug. CRAs and site staff will complete study drug accountability via study drug logs, source documents, subject dosing diaries, empty IP boxes and by visually inspecting the pens/syringes in the sharps container whenever possible. Used sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used pre-filled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the destruction methodology should be maintained at the site's

facility. Unused study drug will be returned by the CRA after drug accountability has been completed at the site.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The design of this clinical trial was chosen to evaluate long-term efficacy, safety, and tolerability, of adalimumab in subjects with CD who participated in and successfully completed Study M14-115.

This is an open-label study.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, endoscopy-related and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CD. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

Subjects who participated and successfully completed Study M14-115 and who meet all of the inclusion criteria and none of the exclusion criteria will be eligible to enroll into this study.

5.6.4 Selection of Doses in the Study

Adalimumab doses were selected based on the US Product Label,[7] in which the recommended adalimumab maintenance dose regimen for adult patients with moderate to severe Crohn's disease is 40 mg eow. In the EU Summary of Product Characteristics,[8] the recommended adalimumab maintenance dose regimen for adult patients with moderate to severe Crohn's disease is 40 mg eow, or 40 mg ew for subjects whose disease is not controlled on 40 mg eow.

6.0 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken. For SAEs 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. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All AEs will be followed to a satisfactory conclusion, including all AEs that are ongoing from Study M14-115.

6.1 Definitions

6.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (see Section 6.7 for toxicity management) and/or if the investigator considers them to be AEs.

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 for Study M14-115. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

6.1.2 Serious Adverse Events

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living 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.

6.2 Adverse Event Severity

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

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.

6.3 Relationship to Study Drug

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

Reasonable Possibility	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 SAE.

6.4 Adverse Event Collection Period

All adverse events including ongoing AEs from Study M14-115, and 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, SAEs will be collected from the time the subject signed the study-specific informed consent. Adverse event information will be collected and recorded on the appropriate eCRFs.

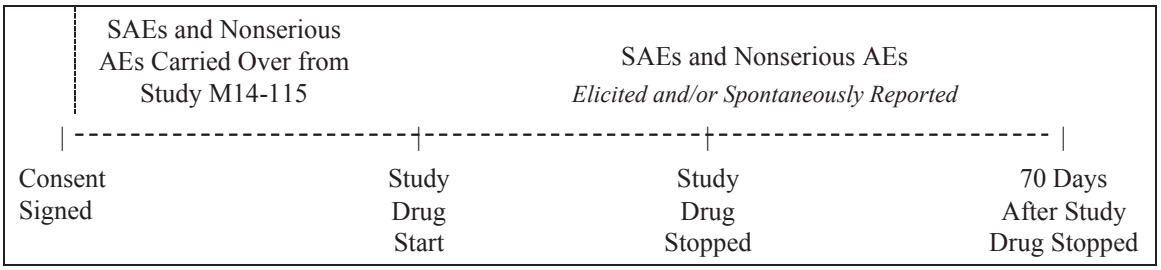
Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects who continue on adalimumab therapy after the end of study participation. These subjects are not required to complete the 70-day follow-up and any new AEs should be reported through the mechanism used for all post-marketing adverse experiences. The 70-day follow-up phone call will be recorded in source document only and confirmation of the contact will be faxed to AbbVie (Appendix J).

All AEs identified to AbbVie from the 70-day follow-up phone call will be collected as source data to be evaluated and reported (Figure 3). Thus, all SAEs and nonserious AEs as defined by AbbVie, reported during the 70-day follow-up phone call must be captured

in the clinical database. The end of trial is the last subject contact, i.e., the 70 day follow-up call.

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

Figure 3. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will notify the AbbVie Clinical Pharmacovigilance and Immunology Safety Management within 24 hours of the physician becoming aware of the event by entering the SAE or nonserious event of malignancy in patients 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the Rave® EDC system or if Rave® is not operable, should be documented on the SAE Non-CRF forms and send to the AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

FAX to:	[redacted]
Email:	[redacted]

For safety concerns, contact the Immunology Safety Management Team at:

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

Primary Study Designated Physician:

Secondary Study Designated Physician:

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

Phone:	[redacted]

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

6.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.2). 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 AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (see Section 6.1 for definitions). Study drug may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use,

every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

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

7.0 Protocol Deviations

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

Primary Contact: Alternate Contact:

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate long-term the efficacy and safety of repeated administration of adalimumab in subjects with Crohn's disease who participated in and successfully complete Study M14-115.

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 Intent-to-treat (ITT) Set and Safety Set consists of all subjects who enrolled into the study and received at least one injection of study drug.

8.1.2 Planned Methods of Statistical Analysis

Descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and counts and percentages for discrete variables. The analysis will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

8.1.3 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics.

8.1.4 Statistical Analyses of Efficacy

8.1.4.1 Primary Efficacy Variable

The primary efficacy variable is proportion of subjects with CD with endoscopic improvement, defined as an SES-CD ≤ 4 with an Ulcerated Surface subscore no greater than 1 in any segment, at Week 40 among the subjects with endoscopic improvement at Week 0 of Study M14-347.

A two-sided 95% confidence interval for the proportion will be calculated. The ITT set includes all subjects who enrolled into this study and received at least one dose of study drug. Missing SES-CD at Week 40 will be imputed using the non-responder imputation (NRI) approach. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses.

8.1.4.2 Additional Efficacy Variables

For categorical additional efficacy endpoints, the two-sided 95% confidence interval for the proportions will be provided. The nonresponder imputation method will be used for subjects with missing data at the time point evaluated. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The LOCF method will also be used as the sensitivity analyses.

For continuous additional efficacy endpoints, change from Baseline of Study M14-347 will be summarized by descriptive statistics using mean, standard deviation, minimum, median and maximum. Both LOCF and observed case analyses will be performed.

For time to event additional efficacy endpoints, the number of event and the 25th, median, and 75th percentiles of time to event will be summarized.

8.1.5 Statistical Analyses of Safety

Laboratory data, AEs, and vital signs are the primary safety parameters in this study. All safety analyses will be performed using the Safety set, which includes all subjects who enrolled into this study and received at least one dose of study drug. Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose of the study drug and within 70 days after the last dose of the study drug. An overview of treatment-emergent AEs, including AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation (see details in the SAP), AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 15.1 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

Changes in laboratory data will be described using statistical characteristics. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used. Vital signs will be analyzed similarly.

8.1.6 Other Statistical Analyses of Efficacy

The subgroups listed below will be used in subgroup analyses of the primary endpoint. The baseline used for the subgroups below is defined as the baseline in Study M14-115.

- Sex (male, female)
- Age (≤ median, > median)
- Race (white, non-white)
- Study M14-115 induction dose (higher, standard)
- Endoscopic improvement status at Week 0 (yes, no)
- CDAI remission status at Week 0 (yes, no)
- SFPS remission status at Week 0 (yes, no)
- Baseline fecal calprotectin [≤ median, > median]
- Baseline fecal calprotectin [≤ 250 µg/g, > 250 µg/g]
- Baseline corticosteroid use (yes, no)

- Baseline immunosuppressant use (yes, no)
- hs-CRP at Baseline (< 10 and ≥ 10 mg/L)
- hs-CRP at Baseline (≤ median, > median)
- Crohn's disease activity (CDAI ≤ 300, > 300) at Baseline
- Baseline CDAI (≤ median, > median)
- Baseline SES-CD [≤ median, > median]
- Prior infliximab use (yes, no)
- Weight (≤ median, > median)
- Baseline albumin (≤ median, > median)
- Disease duration (< 3 years, > 3 years)
- Disease duration (≤ median, > median)

8.1.7 Interim Analysis

An interim analysis of the primary and additional efficacy variables as well as safety data collected will be performed when the results from Study M14-115 are available. A database lock will be performed and any discrepant data will be clarified before the lock.

8.1.8 Pharmacokinetic Analyses

Adalimumab trough serum concentrations will be summarized at each time point using descriptive statistics. In addition, pharmacokinetic model based analyses will be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab. The relationship between adalimumab concentrations and clinical response will be determined as appropriate.

AAA will be evaluated for each subject and each dose, and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent AEs may be evaluated.

8.2 Determination of Sample Size

Approximately 300 subjects who participated in and successfully completed Study M14-115.

9.0 Ethics

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

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

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP.

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

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

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

10.2 Case Report Forms

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from

investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

The following assessments will be completed by subjects on paper:

- IBDQ
- WPAI
- EQ-5D
- Abdominal Pain Rating Scale
- Diary

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

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

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

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

The investigator must 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.

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 Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease
Protocol Date:	04 December 2014

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

1. Hanauer SB, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2001;96(3):635-43.
2. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-17.
3. Probert CS, Jayanthi V, Rampton DS, et al. Epidemiology of inflammatory bowel disease in different ethnic and religious groups: limitations and aetiological clues. Int J Colorectal Dis. 1996;11(1):25-8.
4. Allez M, Lemann M, Bonnet J, et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. A m J Gastroenterol. 2002;97(4):947-53.
5. Froslie KF, Johnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133(2):412-22.
6. Kakkar A, Wasan SK, Farraye FA. Targeting mucosal healing in Crohn's disease. Gastroenterol Hepatol (NY). 2011;7(6):374-80.
7. Humira® (adalimumab) [package insert] North Chicago, IL; AbbVie, 2007.
8. Humira® (adalimumab) [40 mg solution for injection summary of product characteristics package insert] North Chicago, IL; AbbVie, 2007.

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.

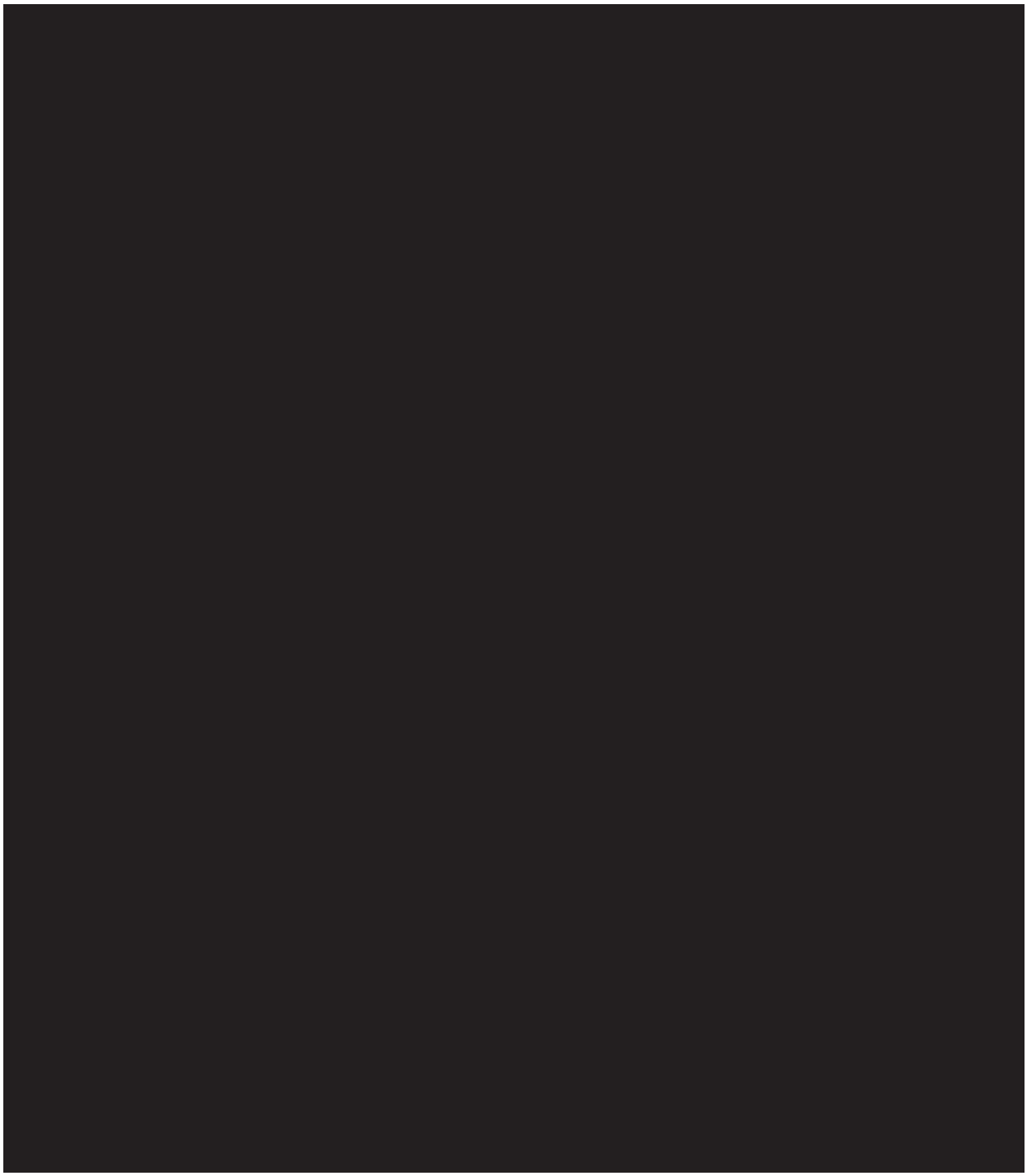
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

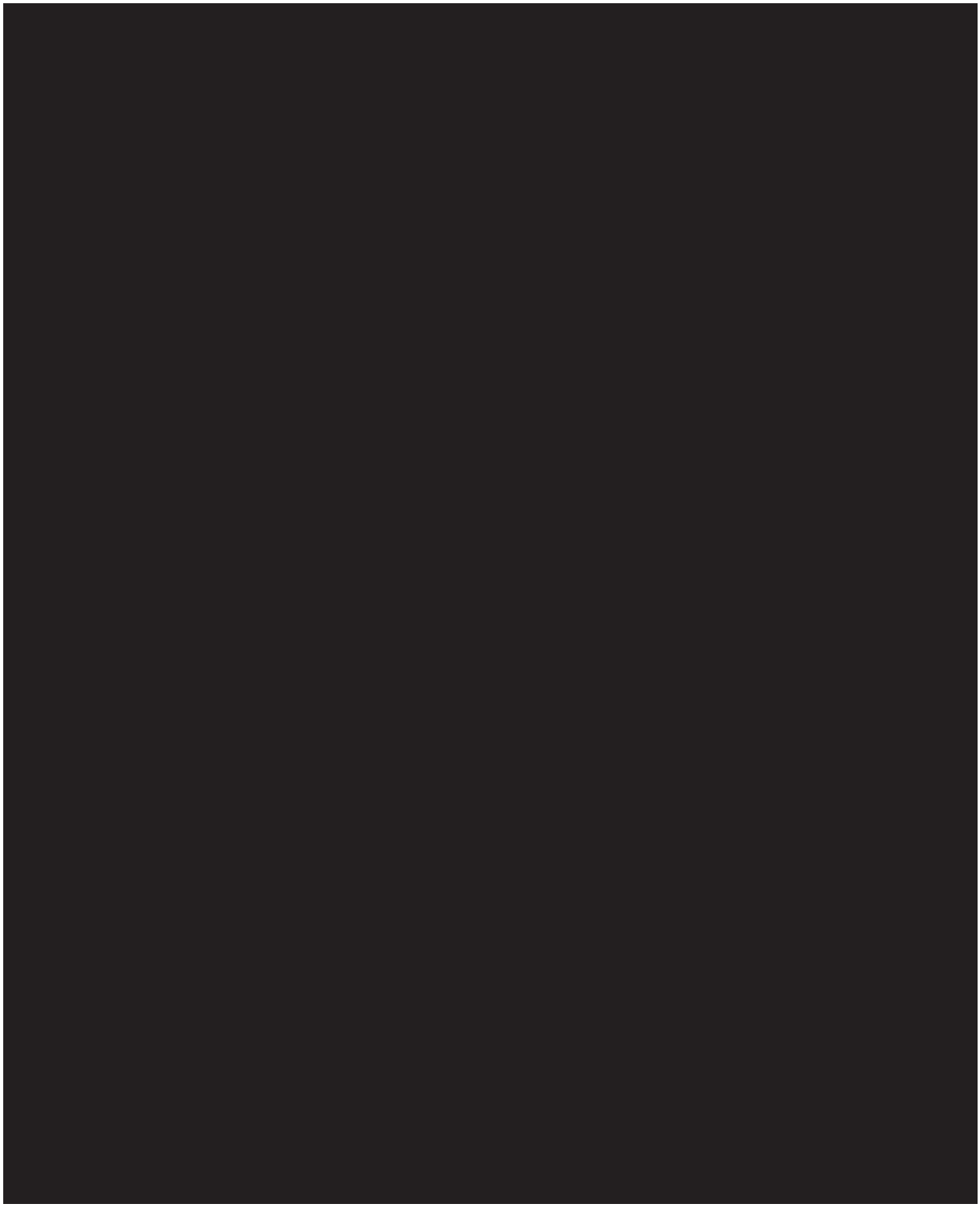
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

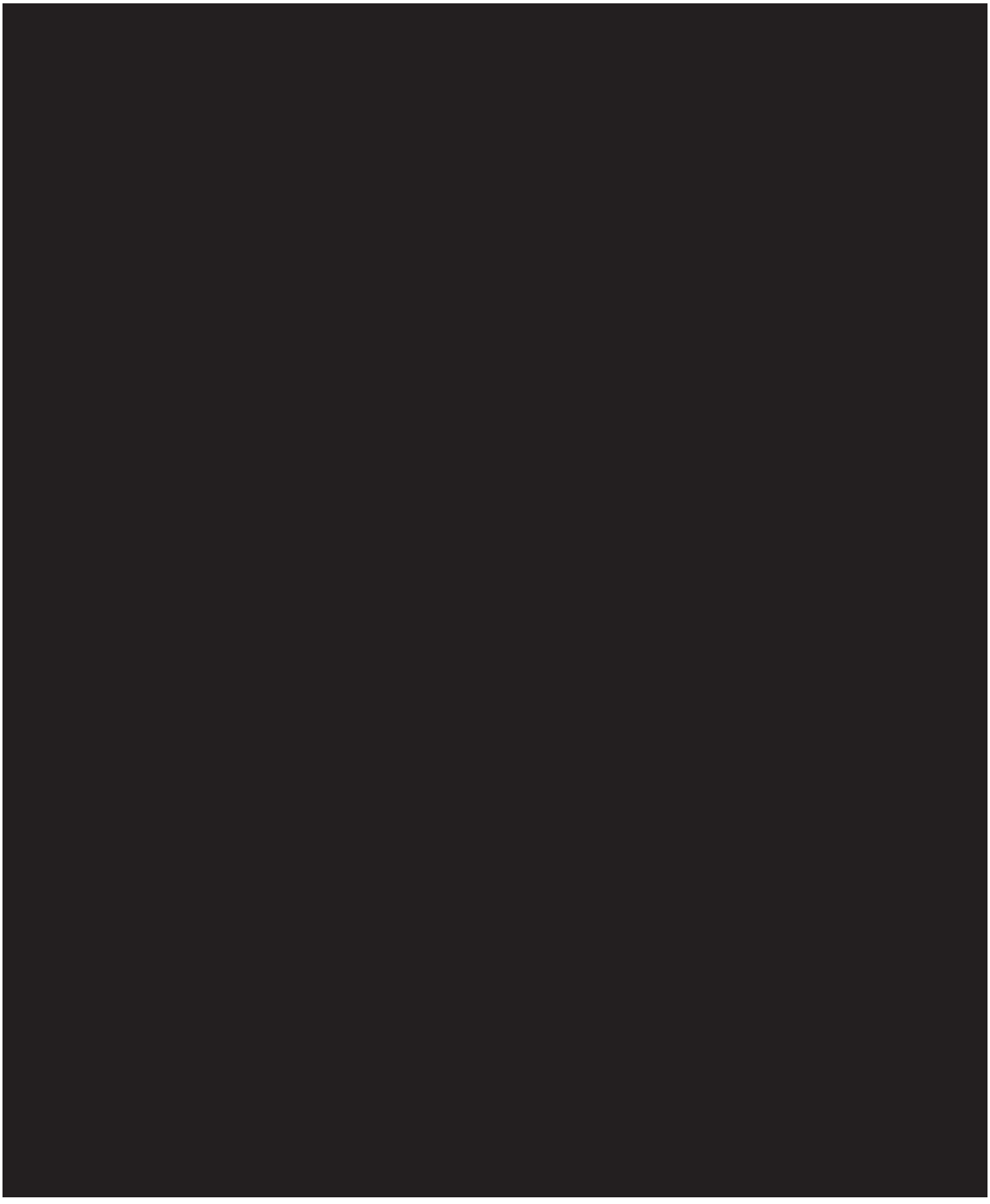
Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical

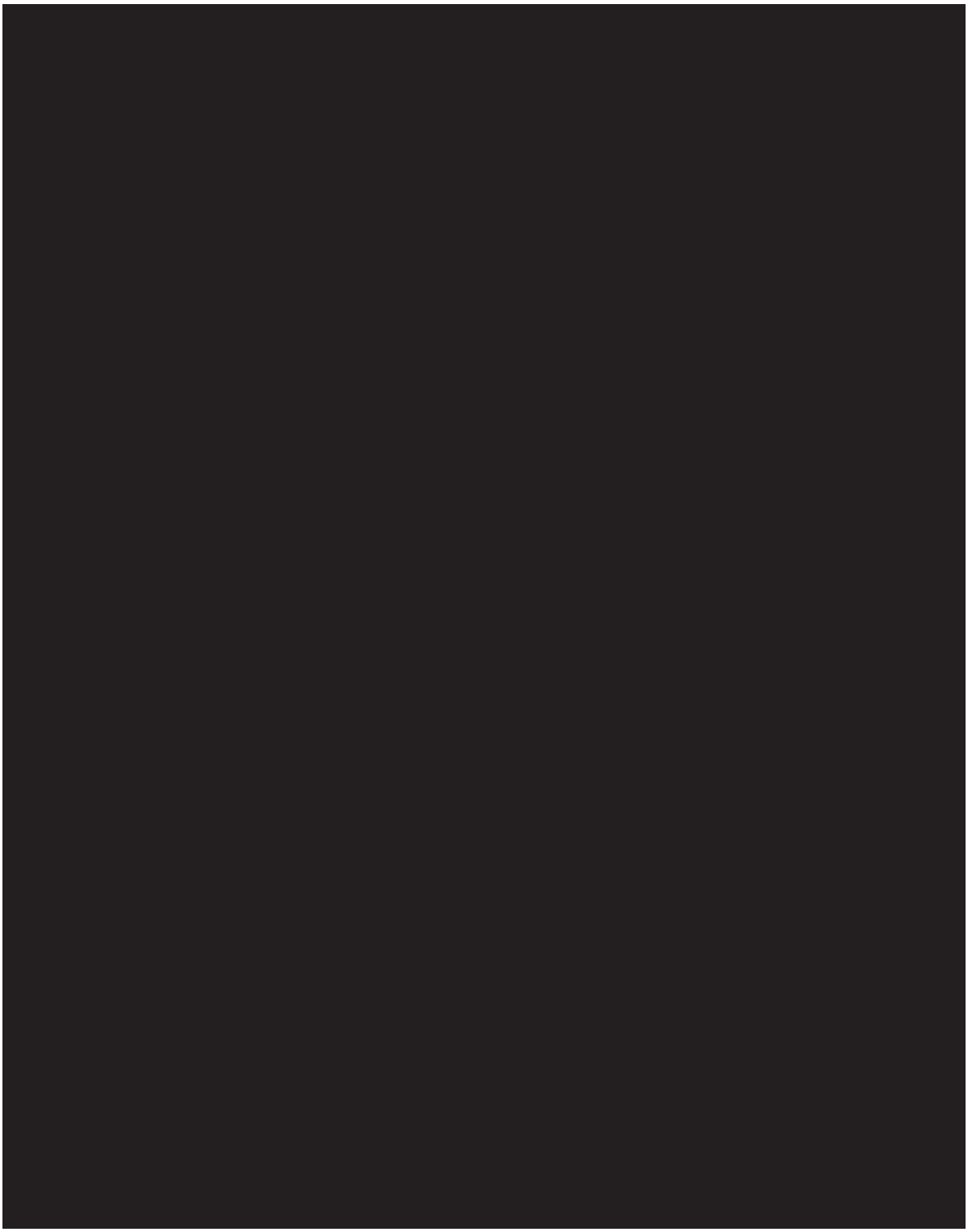
Appendix C. Sample Work Productivity and Activity Impairment Questionnaire: Crohn's Disease V2.0 (WPAI:CD)



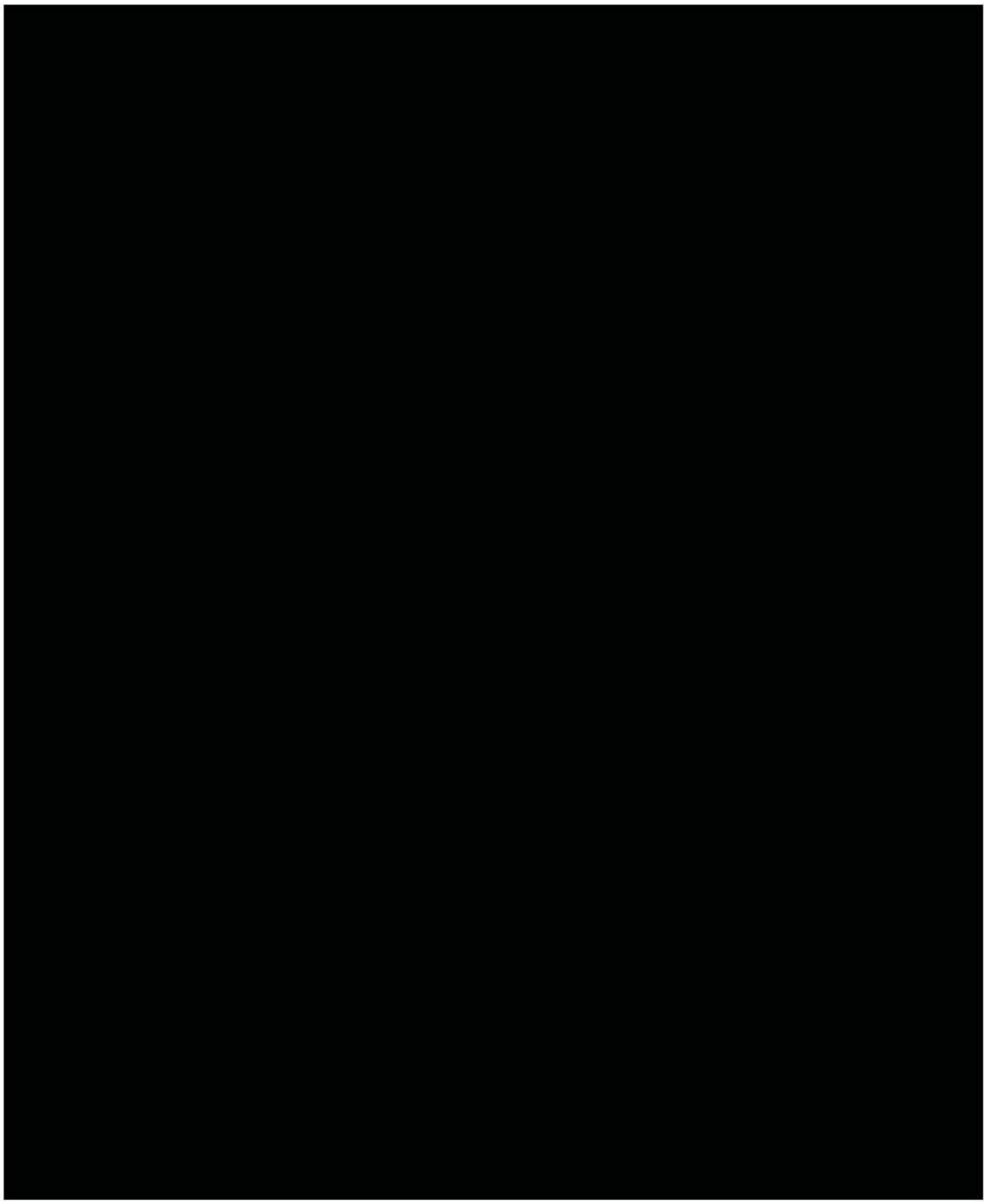


Appendix D. Sample EQ-5D Questionnaires

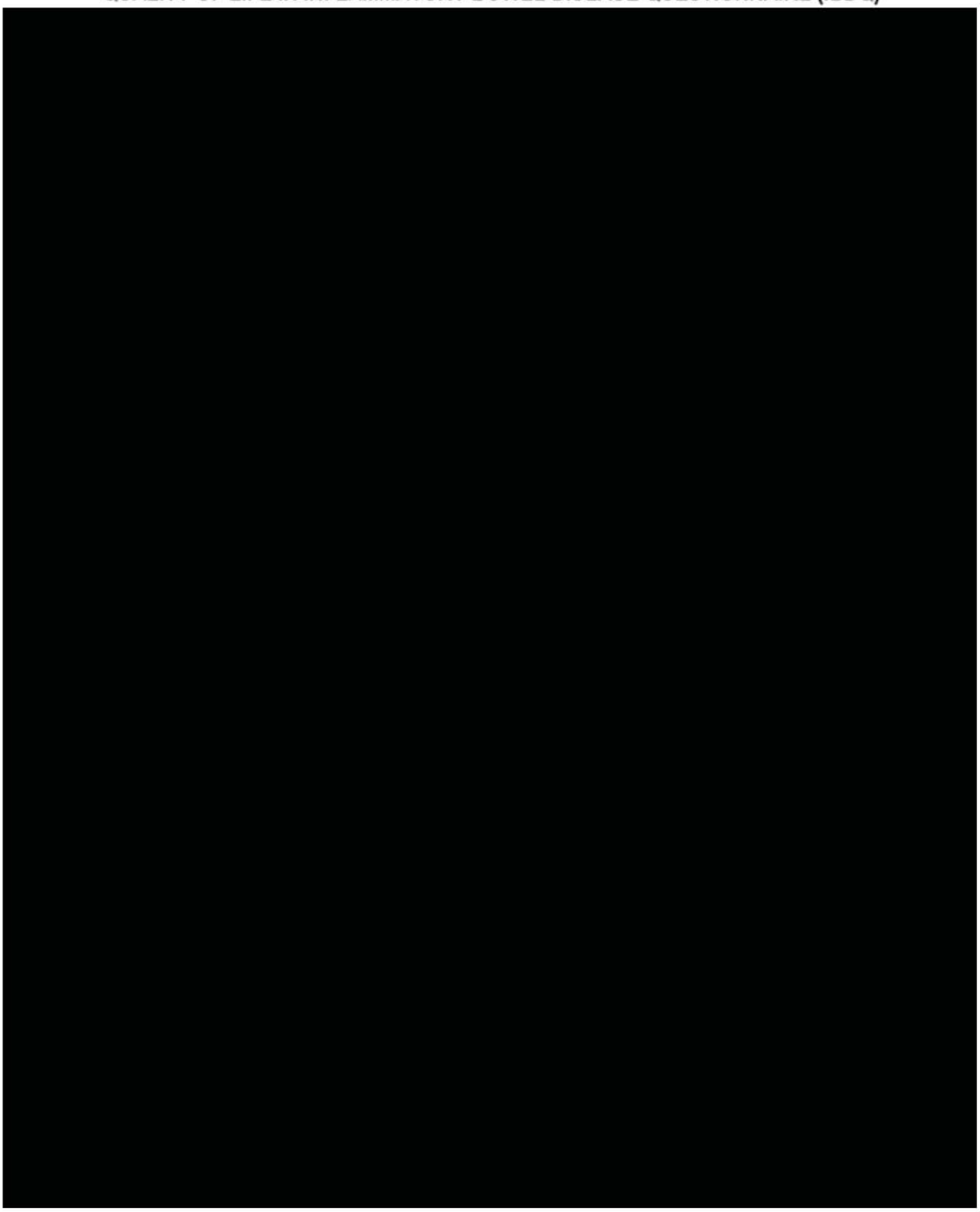


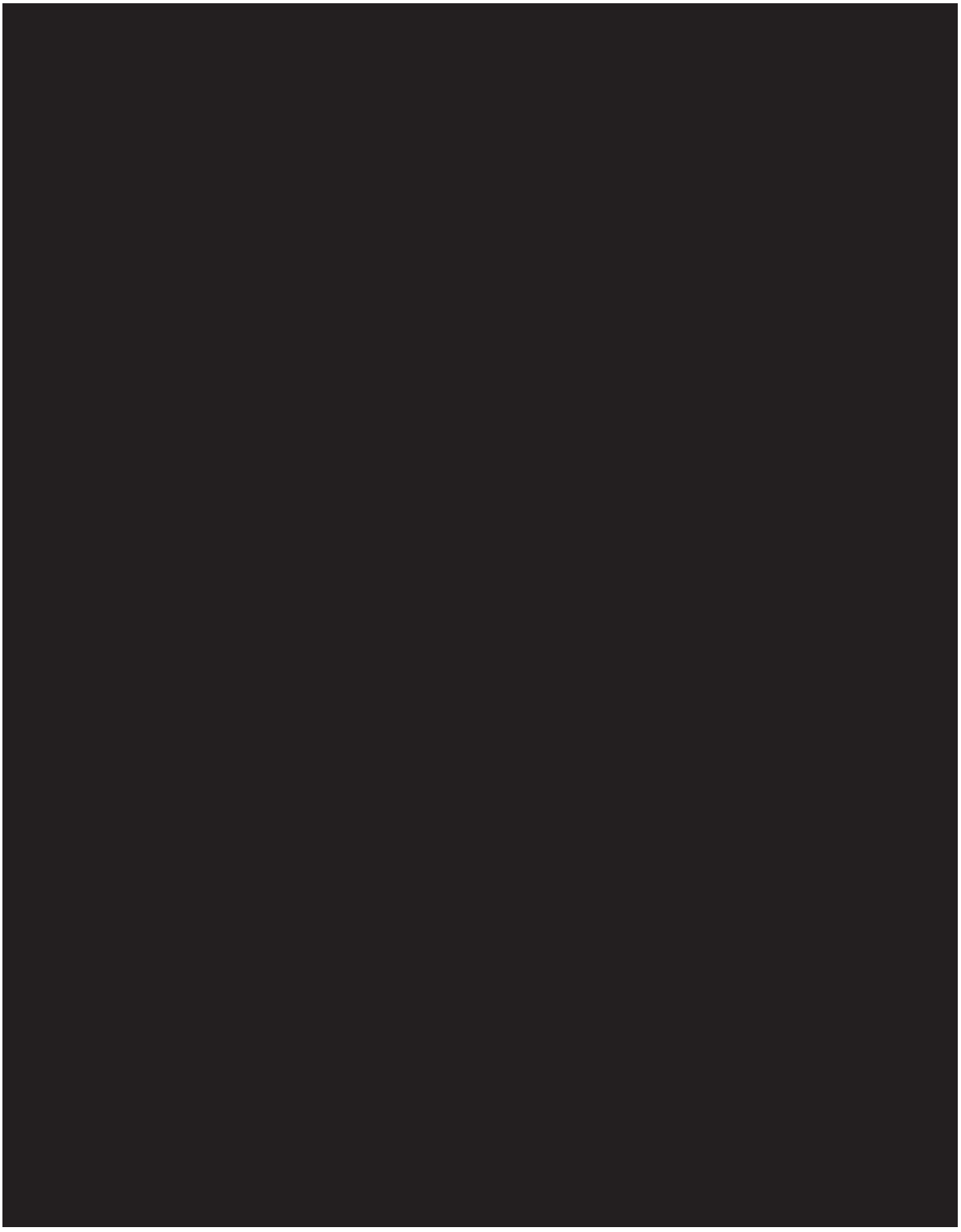


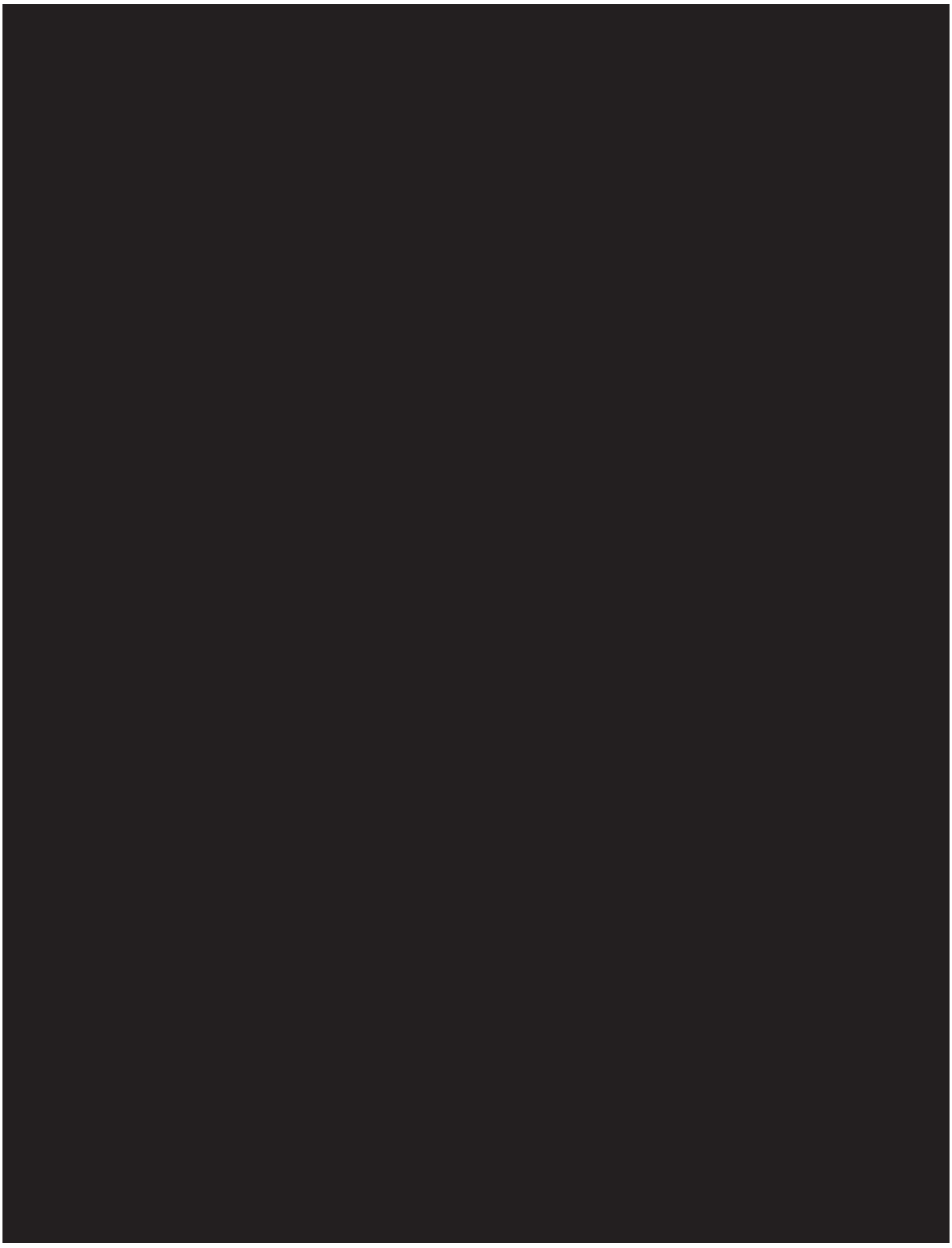
Appendix E. Sample Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ)

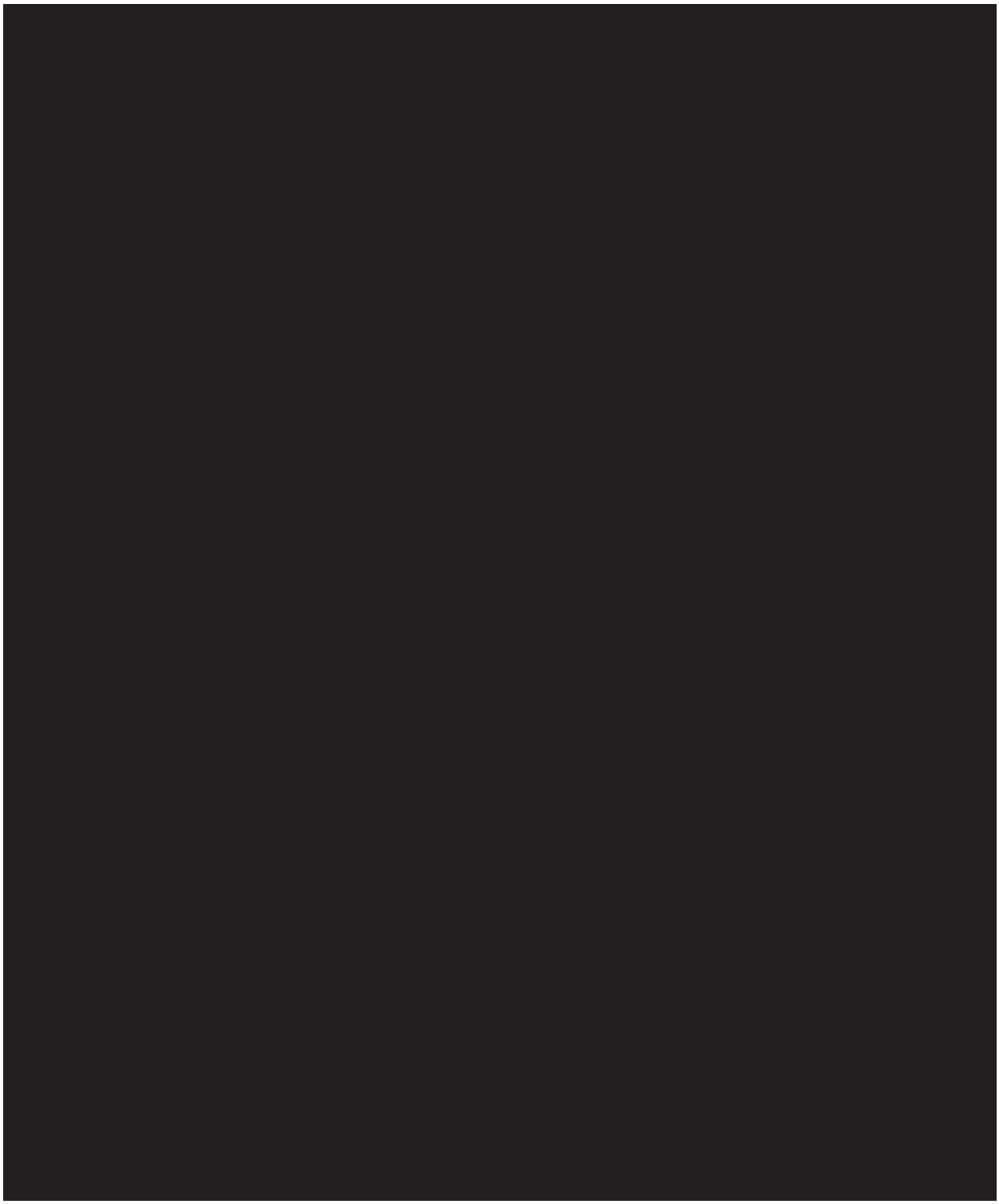


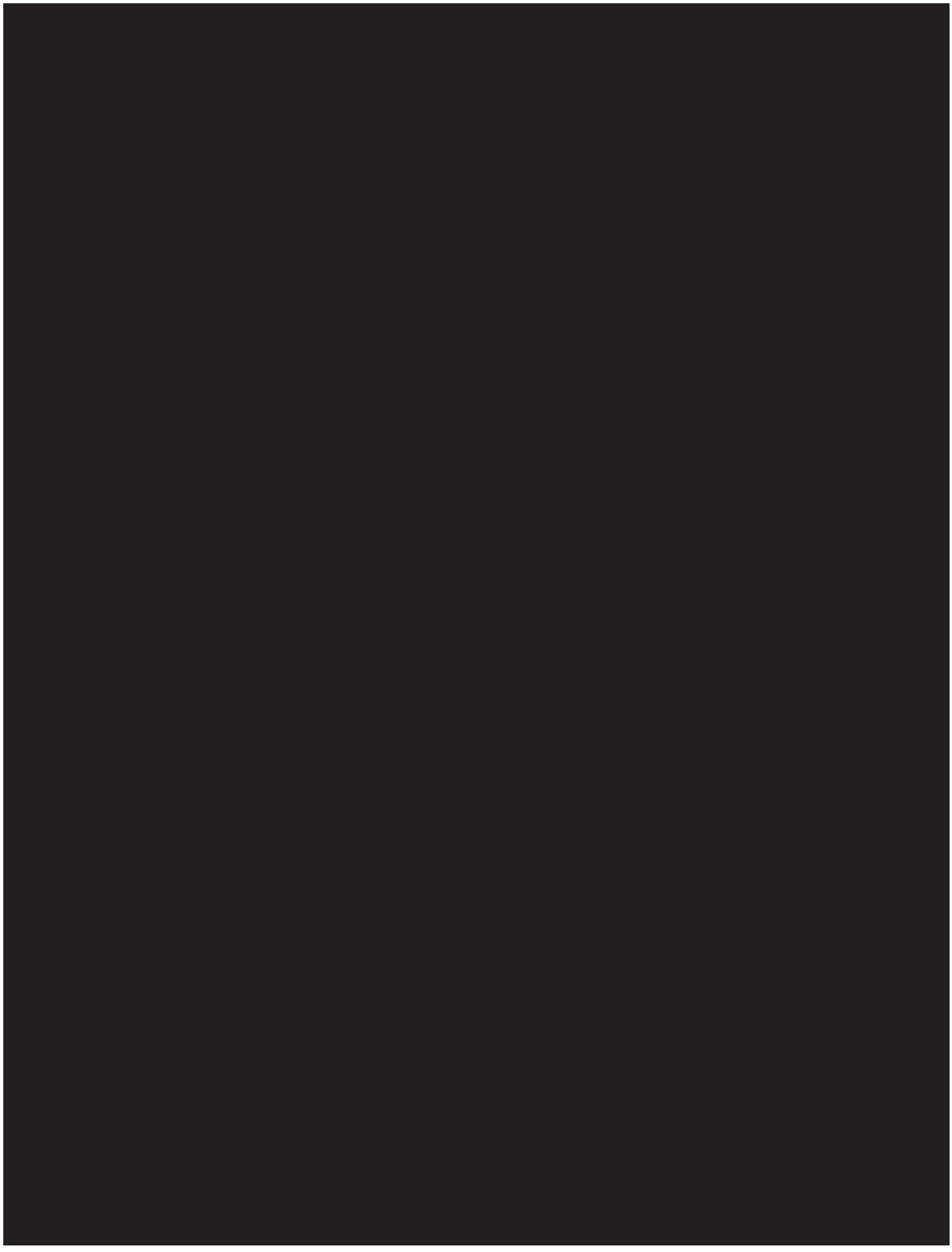
QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

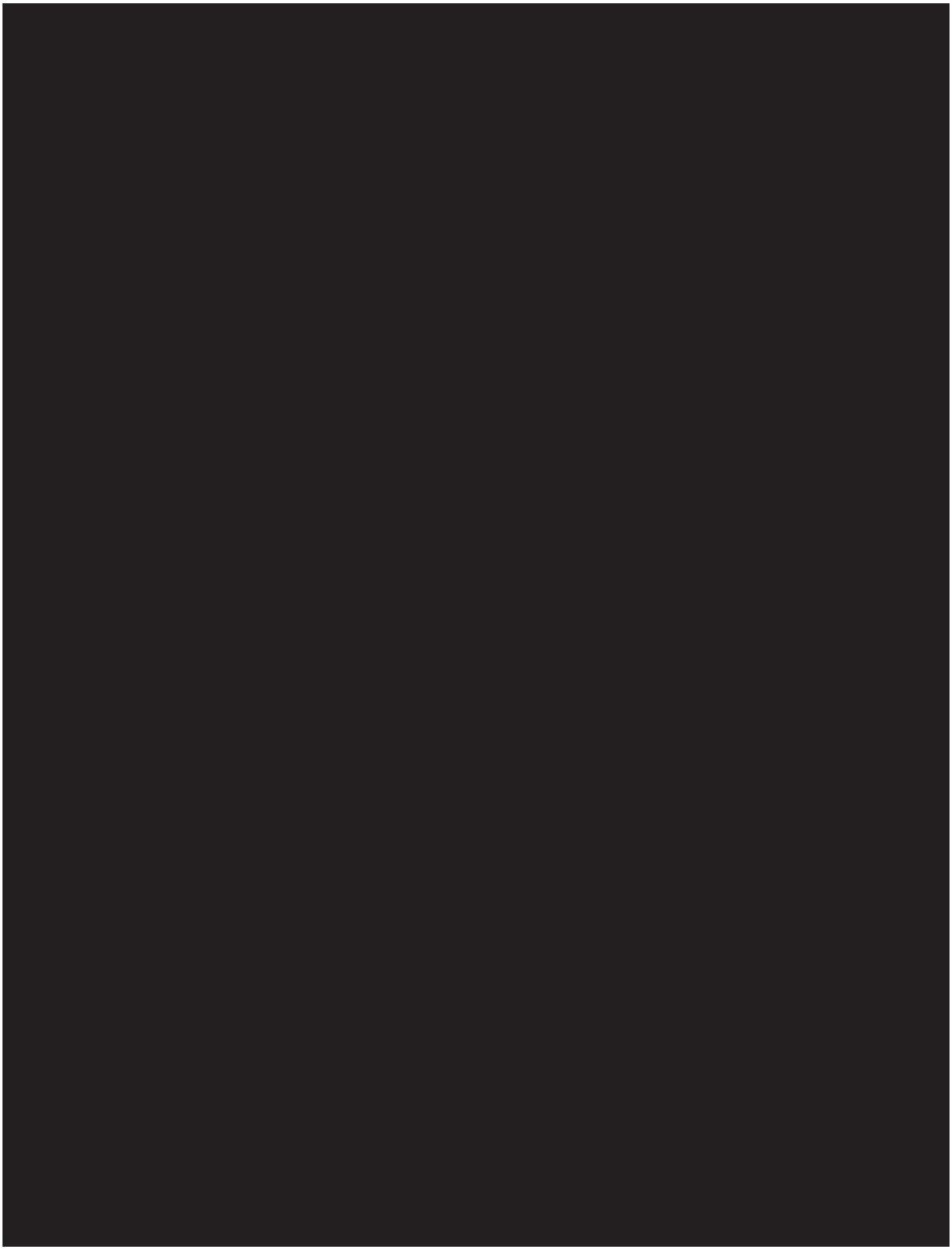


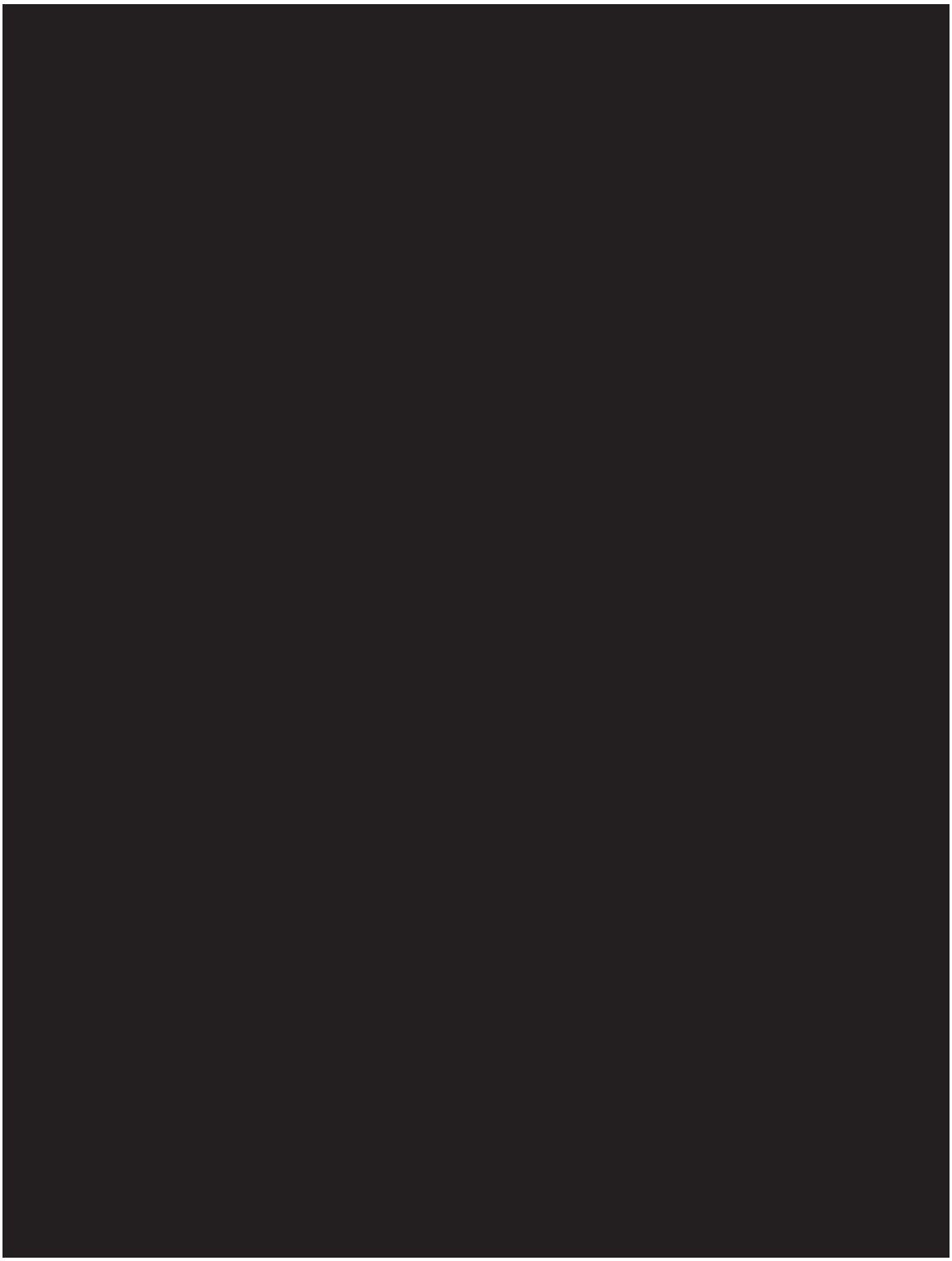


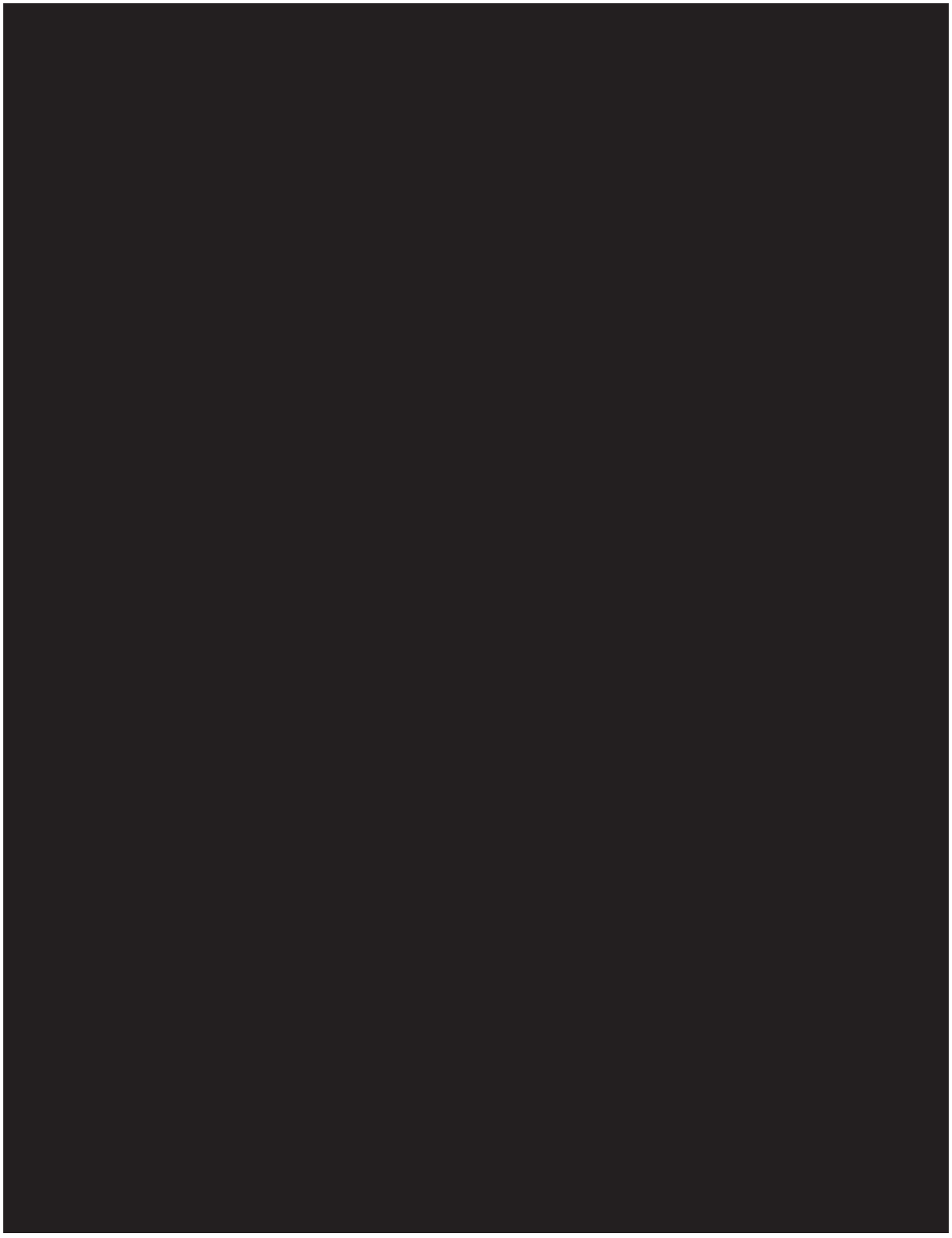


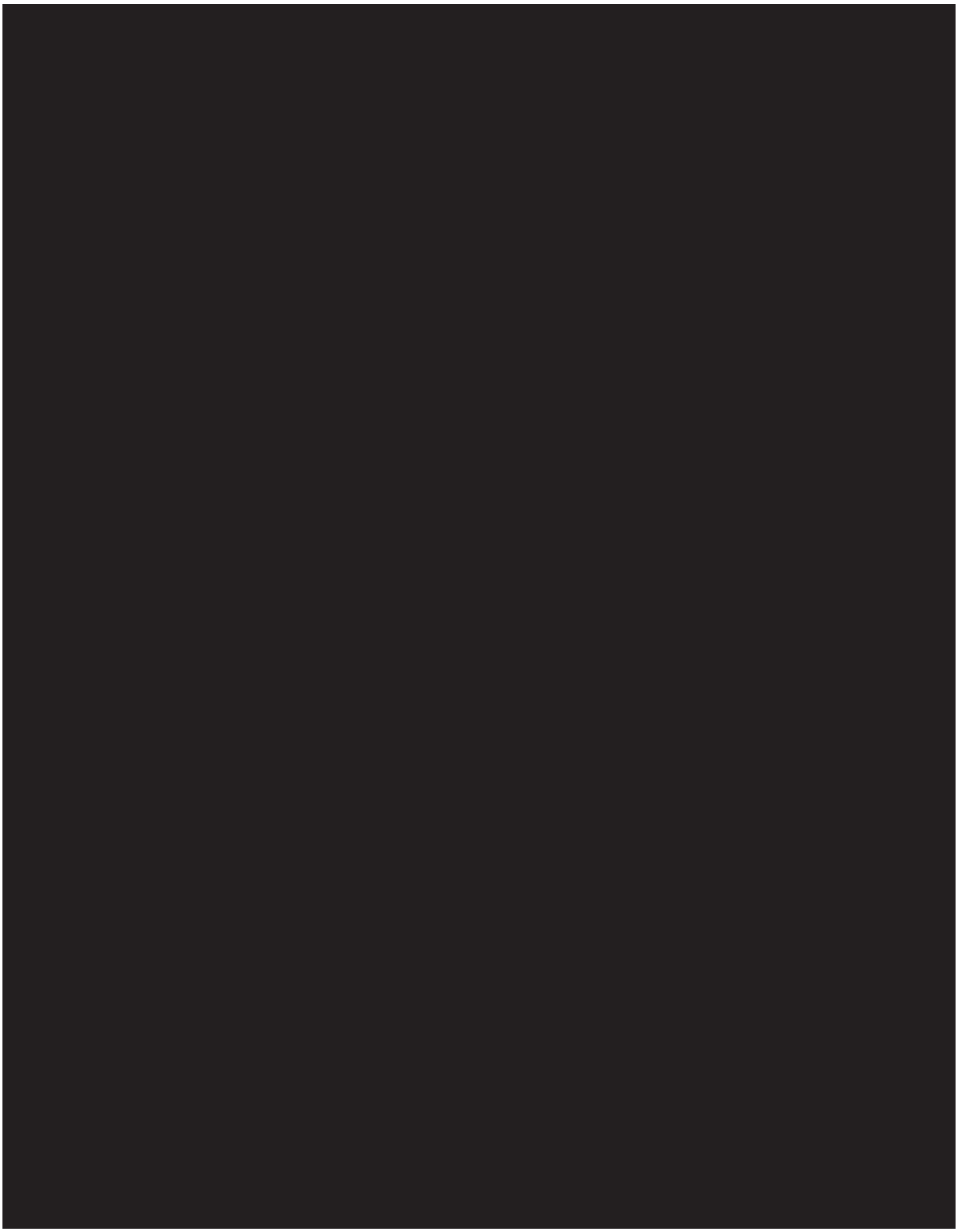




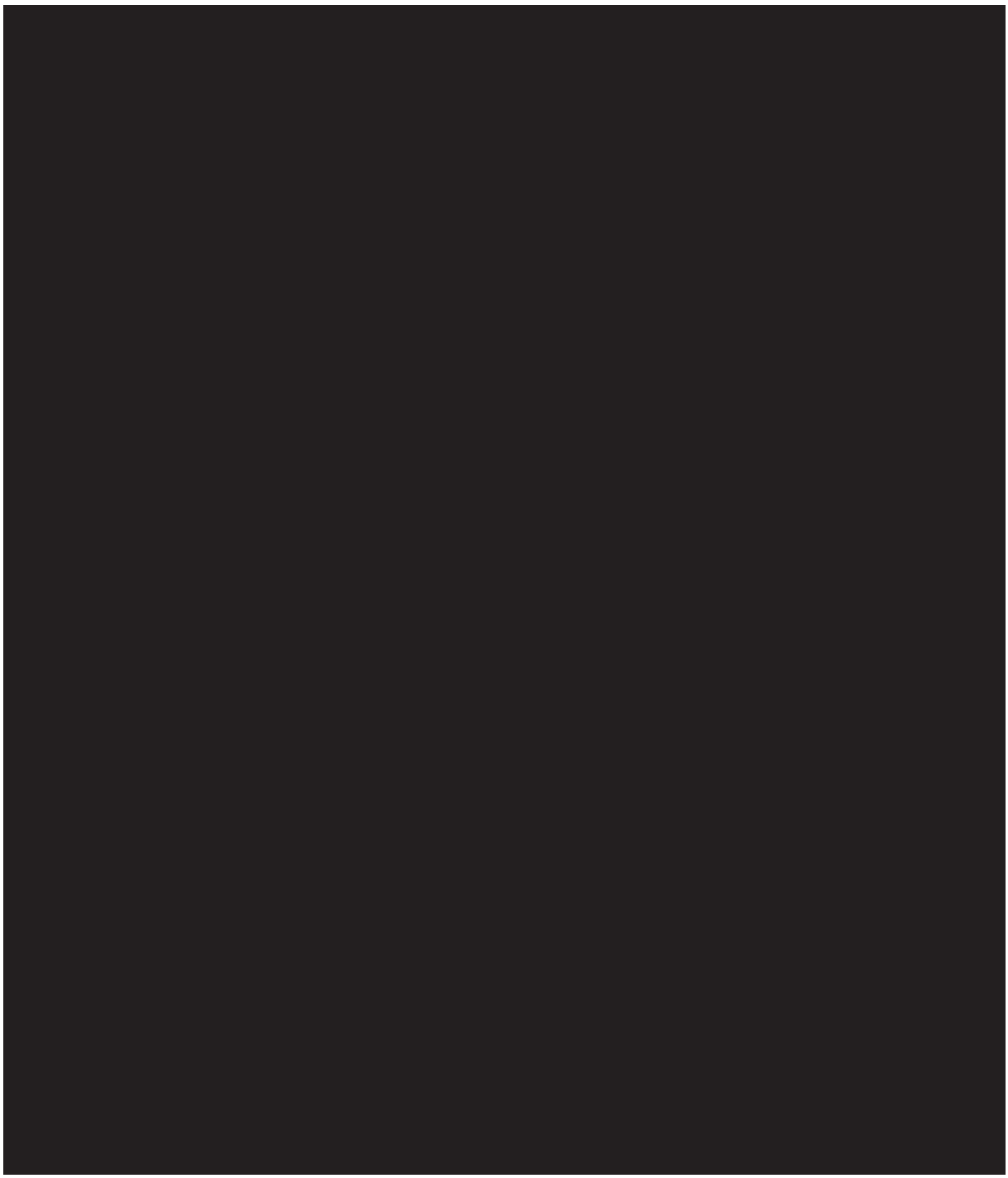








Appendix F. Abdominal Pain Rating Scale



Appendix G. Injection Instructions – Sample Pre-Filled Syringe

Subject Instructions

0.8 mL dose

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

Protocol M14-347

Table of Contents

Study Drug Dosing Schedule

Subject Number: _____

You will require subcutaneous injections throughout the study. Depending how active your Crohn's disease is, your dosing schedule may change. You will receive 1 injection at the clinic at your Baseline Visit (the first visit to receive the study medication for this study).

If your Crohn's disease is under control, then you will take 1 injection every other week. You will receive the following number of injections during the study:

- Weeks 2, 4, 6, 10, 12, 14, 18, 20, 22, 26, 28, 30, 34, 36 and 38 you will administer 1 injection at home.
- At Weeks 8, 16, 24 and 32 you will receive 1 injection at the clinic.

If your Crohn's disease worsens, then your study physician may need to change your dosing schedule and you could begin taking 1 injection every week.

If you feel better at a future visit while taking 1 injection every week, then you may go back to taking 1 injection every other week.

Please return all used and unused syringes and empty boxes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject dosing diary.

Remember to complete your dosing diary after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information

- Pre-filled syringes will be labeled "Adalimumab."
- Store all adalimumab pre-filled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study doctor's office.
- Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY**. There may be medication left in the syringe. **DO NOT RE-USE**.
- Save all study medications. ***Pre-filled syringes (used and unused) & empty boxes must be returned to the study center at each visit***. Used syringes will be disposed of in a sharps container provided to you.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms call _____, or proceed to your nearest emergency room.

Injection Procedures (PFS)

1. Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one kit with the prefilled syringe(s) of adalimumab from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused syringe(s) to the refrigerator.

You will need the following items for each dose:

- study medication in pre-filled syringe(s)

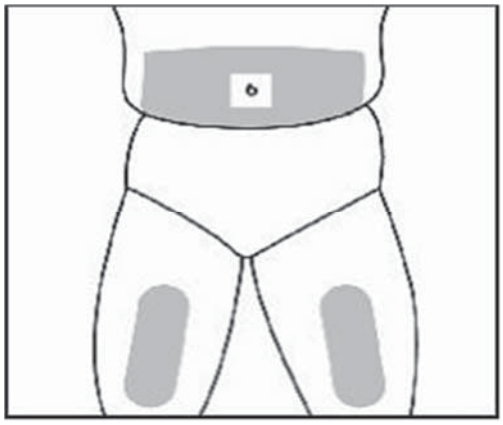
- alcohol prep(s)
- cotton ball or gauze pad(s)

If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

2. Choosing and preparing an injection site



- Wash your hands well.
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.

3. How to prepare your adalimumab dose for injection with a Prefilled Syringe

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg prefilled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay.
- Do not shake the syringe.

4. Injecting Adalimumab

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly.

- You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject adalimumab. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. Do not use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the adalimumab is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container.

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

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

Appendix I. Standard Weights

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

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Actual Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
158.8 (62.5)	62.1 (137.0)	57.4 (126.5)
160.0 (63.0)	62.6 (138.0)	58.0 (128.0)
161.3 (63.5)	63.0 (139.0)	58.7 (129.5)
162.6 (64.0)	63.5 (140.0)	59.4 (131.0)
163.8 (64.5)	64.1 (141.3)	60.1 (132.5)
165.1 (65.0)	64.6 (142.5)	60.8 (134.0)
166.4 (65.5)	65.2 (143.8)	61.4 (135.5)
167.6 (66.0)	65.8 (145.0)	62.1 (137.0)
168.9 (66.5)	66.4 (146.5)	62.8 (138.5)
170.2 (67.0)	67.1 (148.0)	63.5 (140.0)
171.5 (67.5)	67.8 (149.5)	64.2 (141.5)
172.7 (68.0)	68.5 (151.0)	64.9 (143.0)
174.0 (68.5)	69.2 (152.5)	65.5 (144.5)
175.3 (69.0)	69.8 (154.0)	66.2 (146.0)
176.5 (69.5)	70.5 (155.5)	66.9 (147.5)
177.8 (70.0)	71.2 (157.0)	67.6 (149.0)
179.1 (70.5)	71.9 (158.5)	68.3 (150.5)
180.3 (71.0)	72.6 (160.0)	68.9 (152.0)
181.6 (71.5)	73.4 (161.8)	69.6 (153.5)
182.9 (72.0)	74.1 (163.5)	70.3 (155.0)
184.2 (72.5)	75.0 (165.3)	71.2 (156.9)
185.4 (73.0)	75.7 (167.0)	71.9 (158.5)
186.7 (73.5)	76.6 (169.0)	72.6 (160.2)
188.0 (74.0)	77.5 (171.0)	73.4 (161.8)
189.2 (74.5)	78.4 (172.8)	74.1 (163.4)
190.5 (75.0)	79.1 (174.5)	74.9 (165.1)
191.8 (75.5)	80.2 (176.8)	75.6 (166.8)
193.0 (76.0)	81.2 (179.0)	71.2 (156.9)
194.3 (76.5)	82.0 (180.8)	77.2 (170.1)
195.6 (77.0)	82.9 (182.9)	77.9 (171.8)
196.9 (77.5)	83.9 (185.0)	78.7 (173.5)

Standard Height and Weight Tables – Use to Calculate CDAI Score		
Actual Height cm (Inches)	**Standard Weight (Men) kg (Pounds)**	**Standard Weight (Women) kg (Pounds)**
198.1 (78.0)	84.9 (187.2)	79.5 (175.2)
199.4 (78.5)	85.9 (189.4)	80.3 (177.0)
200.7 (79.0)	86.9 (191.6)	81.0 (178.7)
201.9 (79.5)	87.9 (193.9)	81.8 (180.5)
203.2 (80.0)	89.0 (196.2)	82.6 (182.2)
204.5 (80.5)	90.0 (198.6)	*Height in shoes with one inch heels
205.7 (81.0)	91.1 (200.9)	*Indoor clothing weighing 5 pounds for men and 3 pounds for women
207.0 (81.5)	92.2 (203.3)	*Centimeters × 0.3937 = inches
208.3 (82.0)	93.3 (205.8)	*Pounds × 0.4535 = kilograms

Appendix J. 70-Day Follow-Up Phone 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 one attempt.)
- ☐ No Events Reported
- ☐ N/A subject continued adalimumab therapy after the end of their study participation

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

_____

_____

_____

_____

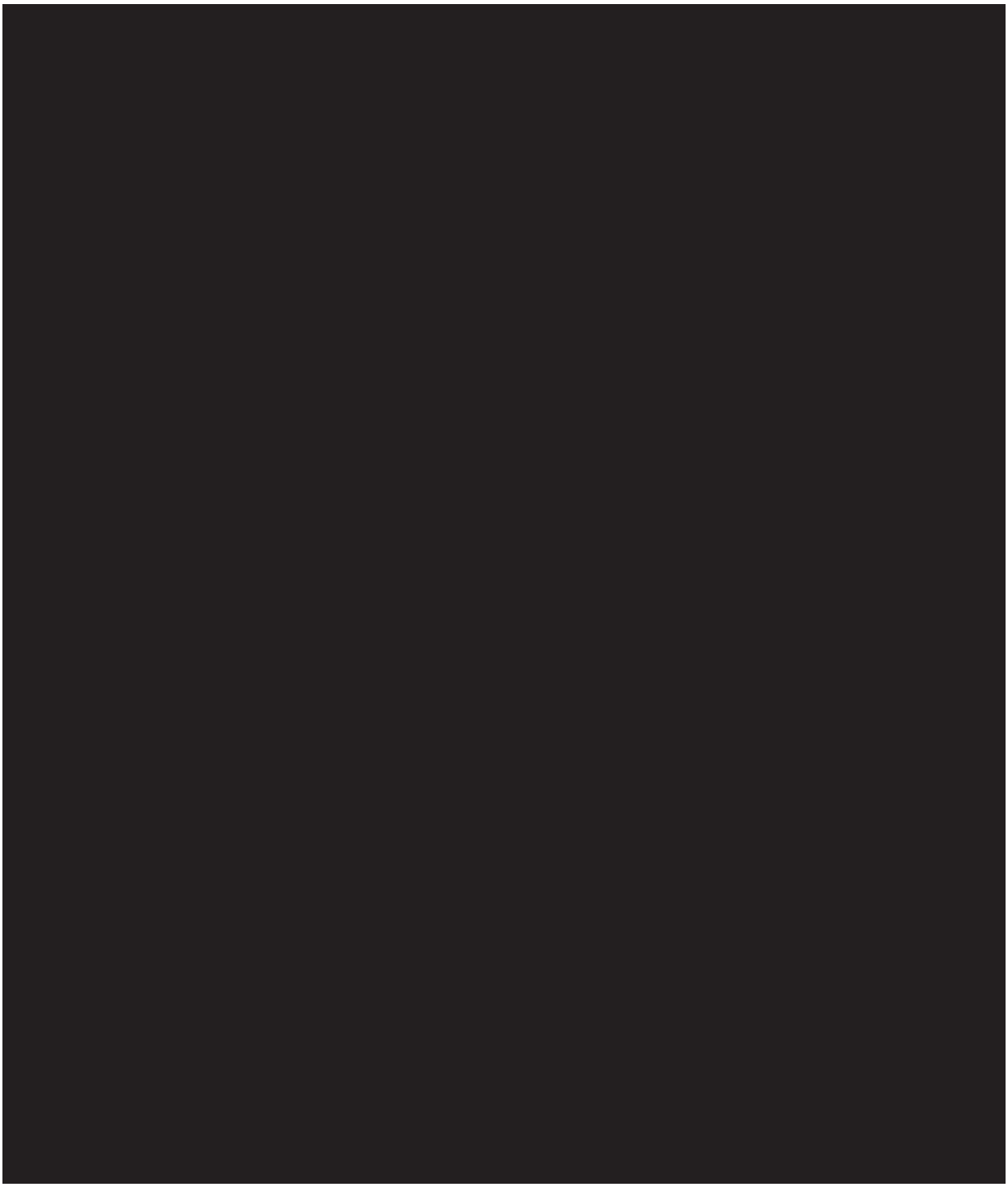
_____

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

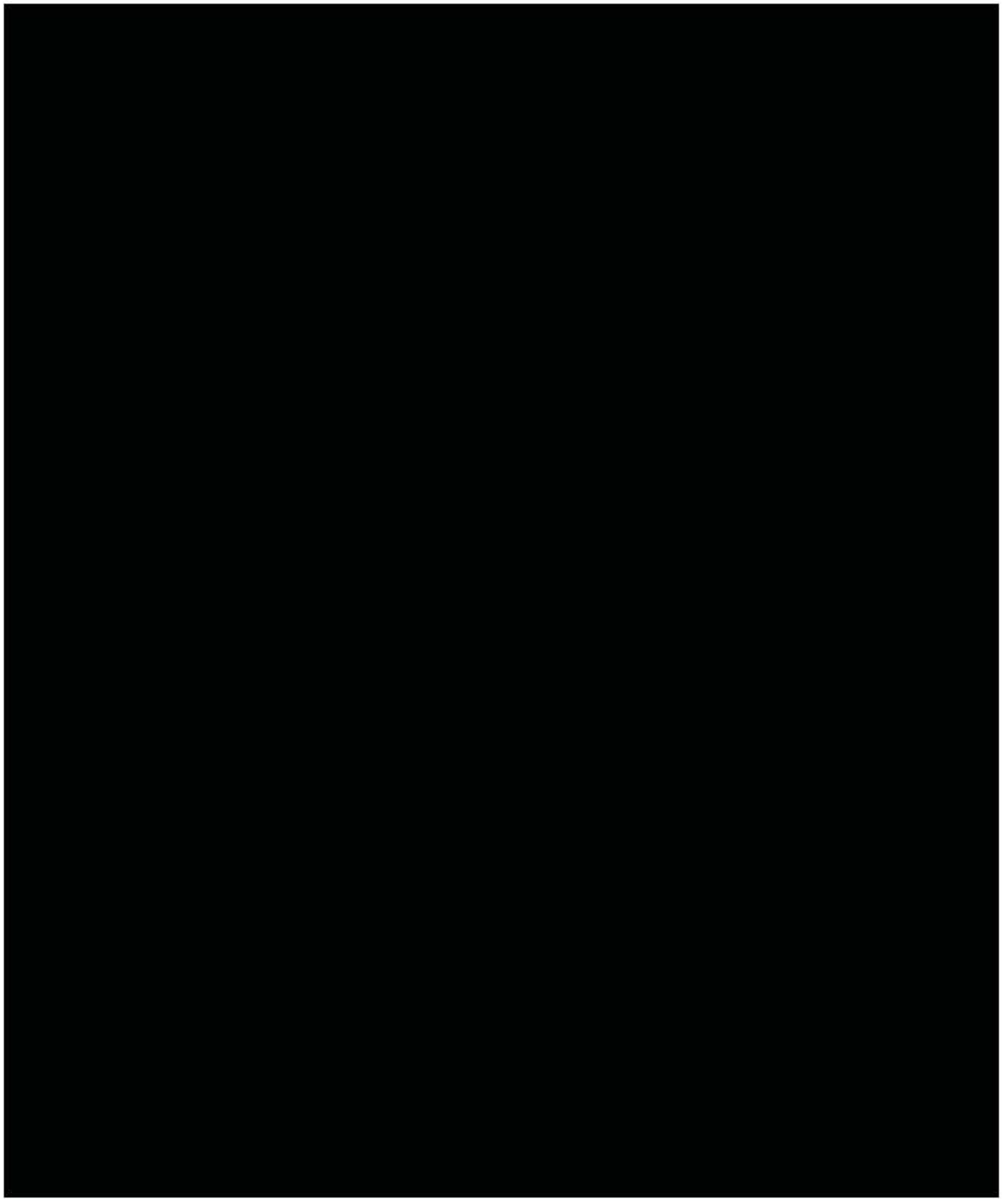
Please fax all completed forms to:

[Name] at XXX-XXX-XXXX

Appendix K. SES-CD Scoring



Appendix L. Bristol Stool Form Scale



Appendix M. Protocol Amendment: List of Changes

Specific Protocol Changes:

The summary of changes is listed in Section 1.1.

Section 1.2 Synopsis
Subsection Methodology:
Second paragraph, last sentence previously read:

Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 2 should the subject meet the criteria for inadequate response:

Has been changed to read:

Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 1 should the subject meet the criteria for inadequate response:

Section 1.2 Synopsis
Subsection Methodology:
Heading "Inadequate Response:"
First paragraph, first sentence previously read:

Crohn's disease activity index (CDAI) ≥ 200 for two consecutive visits that are at least fourteen (14) days apart, and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or a hs-CRP ≥ 5 mg/L.

Has been changed to read:

Crohn's disease activity index (CDAI) ≥ 200 at any one visit and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L. The hs-CRP results used to determine inadequate response can be from the prior or current visit.

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Efficacy:"
Subheading "Additional Efficacy Endpoints:"
Seventh bullet previously read:

- Proportion of subjects who require weekly dosing at Week 2 of Study M14-347.

Has been changed to read:

- Proportion of subjects who require weekly dosing at Week 1 of Study M14-347.

Section 5.1 Overall Study Design and Plan: Description
Fourth paragraph, last sentence previously read:

Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 2 should the subject meet the criteria for inadequate response (Table 1).

Has been changed to read:

Subjects may be escalated to adalimumab 40 mg every week (ew) at or after Week 1 should the subject meet the criteria for inadequate response (Table 1).

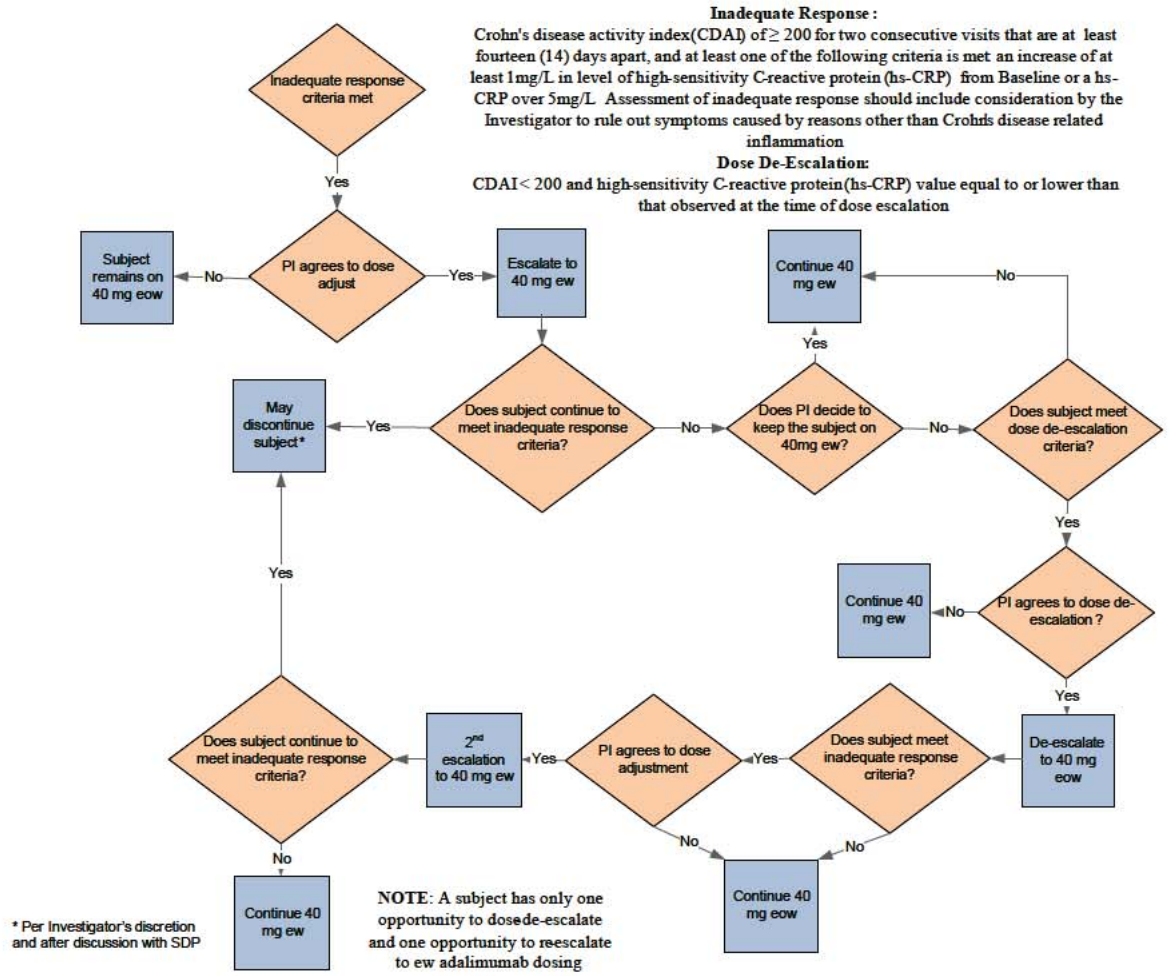
Table 1. Inadequate Response
Previously read:

Response Type	Definition
Inadequate response	Crohn's disease activity index (CDAI) of ≥ 200 for two consecutive visits that are at least fourteen (14) days apart, and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or a hs-CRP ≥ 5 mg/L. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.

Has been changed to read:

Response Type	Definition
Inadequate response	Crohn's disease activity index (CDAI) of ≥ 200 at any one visit and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L. The hs-CRP results used to determine inadequate response can be from the prior or current visit. Assessment of inadequate response should include consideration by the Investigator to rule out symptoms caused by reasons other than Crohn's disease related inflammation.

Figure 1. Dose Adjustment Algorithm
Previously read:



Has been changed to read:

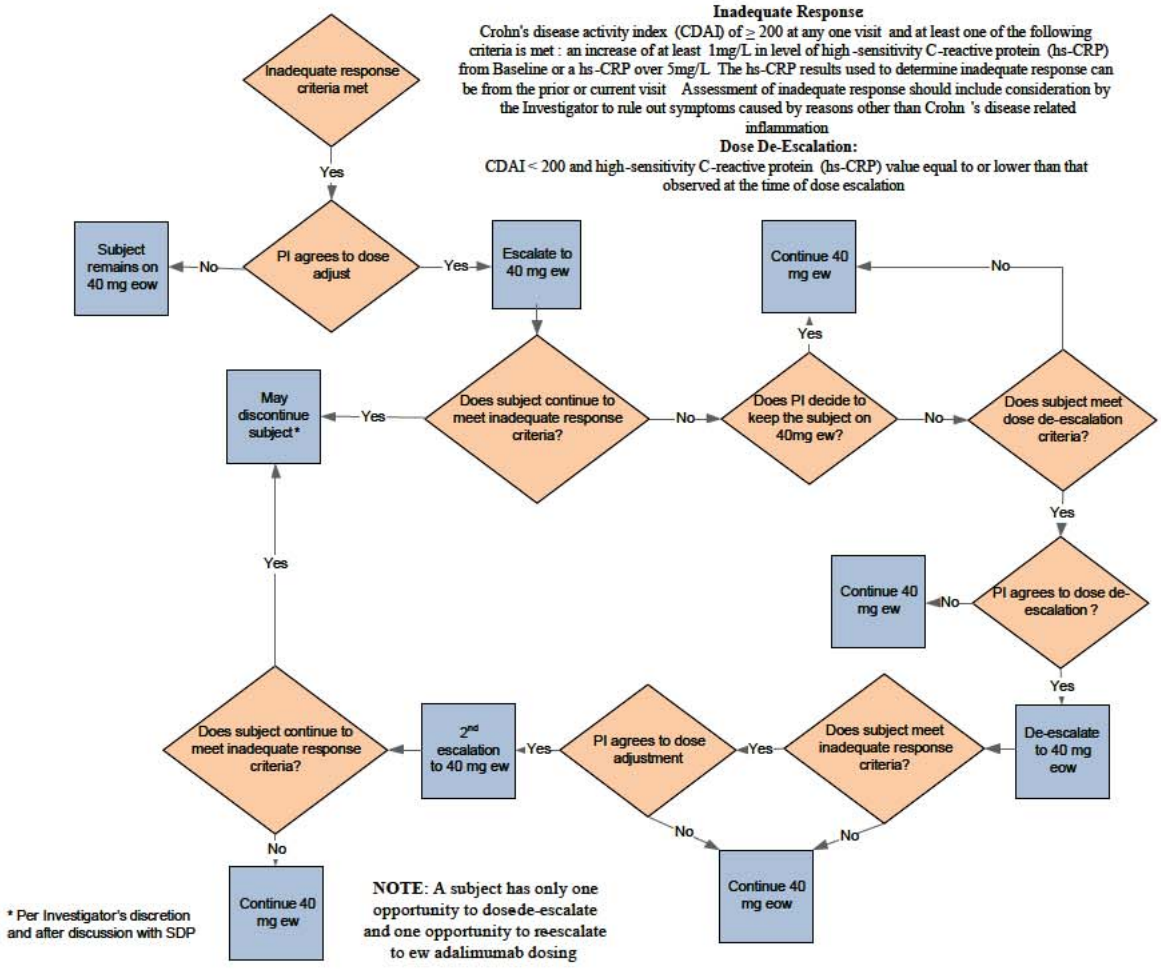


Table 2. Study Activities
Row "Serological Biomarkers/mRNA" previously read:

Activity	Baseline (Week 0)[a]	Week 8	Week 16	Week 24	Week 32	Week 40/ Premature Discontinuation	Unscheduled Visit[k]	70-Day Follow-Up Call[l]
Serological Biomarkers/mRNA	X[a]			X		X	X	

Has been changed to read:

Activity	Baseline (Week 0)[a]	Week 8	Week 16	Week 24	Week 32	Week 40/ Premature Discontinuation	Unscheduled Visit[k]	70-Day Follow-Up Call[l]
Serological Biomarkers/mRNA	X[a]			X		X		

Table 2. Study Activities
Row "Inflammatory Bowel disease Questionnaire (IBDQ)" through row "Abdominal Pain Rating Scale" previously read:

Activity	Baseline (Week 0)[a]	Week 8	Week 16	Week 24	Week 32	Week 40/ Premature Discontinuation	Unscheduled Visit[k]	70-Day Follow-Up Call[l]
Inflammatory Bowel disease Questionnaire (IBDQ)	X[a]		X		X	X	X	
European Quality of Life 5 dimensions (EQ-5D)	X[a]		X		X	X	X	
Work Productivity and Impairment Questionnaire (WPAI)	X[a]		X		X	X	X	
Abdominal Pain Rating Scale	X[a]		X		X	X	X	

Has been changed to read:

Activity	Baseline (Week 0)[a]	Week 8	Week 16	Week 24	Week 32	Week 40/ Premature Discontinuation	Unscheduled Visit[k]	70-Day Follow-Up Call[l]
Inflammatory Bowel disease Questionnaire (IBDQ)	X[a]		X		X	X		
European Quality of Life 5 dimensions (EQ-5D)	X[a]		X		X	X		
Work Productivity and Impairment Questionnaire (WPAI)	X[a]		X		X	X		
Abdominal Pain Rating Scale	X[a]		X		X	X		

Table 2. Study Activities
Table note "g." last sentence previously read:

Stool samples for metagenomic analysis should be collected before any bowel preparation for endoscopy is started and returned to the site within 2 days of collection.

Has been changed to read:

Stool samples for metagenomic analysis should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection.

Table 2. Study Activities
Table note "k." previously read:

Visits for dispensing new study drug in case of temperature excursion, loss, or damage are not considered an Unscheduled Visit. In addition, visits to retest a lab will not be considered an Unscheduled Visit. Unscheduled visits can be used for situations including the following: For evaluation and assessment of the subject, to dispense study drug, to evaluate a subject who meets criteria for inadequate response as outlined in Table 1, to collect samples to determine hs-CRP in those subjects, and to collect PK samples for a change in adalimumab dosing.

Has been changed to read:

Visits for dispensing new study drug in case of temperature excursion, loss, damage, or dose escalation are not considered an Unscheduled Visit. In addition, visits to retest a lab will not be considered an Unscheduled Visit. Unscheduled visits can be used for situations including the following: For evaluation and assessment of the subject, to evaluate a subject who meets criteria for inadequate response as outlined in Table 1, to collect samples to determine hs-CRP in those subjects, and to collect PK samples for a change in adalimumab dosing.

Section 5.3.1.1 Study Procedures
Subsection Informed Consent
Add: new last sentence

Consent will be required for any optional testing.

Section 5.3.1.1 Study Procedures
Subsection Endoscopy
Second paragraph, first sentence previously read:

An ileocolonoscopy will be performed and recorded at the site in a video format.

Has been changed to read:

An ileocolonoscopy will be performed and should be recorded at the site in a video format.

Section 5.3.1.1 Study Procedures
Subsection Urinalysis
Last sentence previously read:

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.

Has been changed to read:

Microscopic urinalysis will only be performed by the central laboratory if the dipstick UA results are abnormal, where abnormal is defined as a protein, ketones or blood greater than negative or glucose greater than normal.

Section 5.3.1.1 Study Procedures
Subsection Other Laboratory Assessments
Heading "Stool Sample (Fecal Calprotectin and Microbiota Metagenomic Analyses)"
Second paragraph, first sentence previously read:

All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site within 2 days of collection.

Has been changed to read:

All stool samples should be collected before any bowel preparation for endoscopy is started and returned to the site within 3 days of collection.

Section 5.3.1.1 Study Procedures
Subsection Other Laboratory Assessments
Heading "Stool Sample (Fecal Calprotectin and Microbiota Metagenomic Analyses)"
Third paragraph, first sentence previously read:

Any remaining stool could be used for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or development of AEs.

Has been changed to read:

Where allowed by local guidelines at the time of stool collection any remaining stool could be used for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug or additional therapies, or development of AEs.

Section 5.3.3.2 Additional Efficacy Variables
Seventh bullet previously read:

- Proportion of subjects who require weekly dosing at Week 2 of Study M14-347.

Has been changed to read:

- Proportion of subjects who require weekly dosing at Week 1 of Study M14-347.

Section 6.5 Adverse Event Reporting
"Primary Study Designated Physician:" contact information previously read:

Has been changed to read:

Section 6.5 Adverse Event Reporting
Fifth paragraph and contact information previously read:

Back-Up Study Designated Physician:

[redacted]

Has been changed to read:

Secondary Study Designated Physician:

[redacted]

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

Phone: [redacted]

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical
		Clinical
		Clinical

Document Approval

Study M14347 - A Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease - Amendment 2 - EudraCT 2013-004034-15 - 04Dec2014

Version: 1.0 **Date:** 05-Dec-2014 11:07:09 PM **Abbott ID:** 12052014-00F9F680AFF645-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	04-Dec-2014 06:08:41 PM	Approver
	04-Dec-2014 06:20:51 PM	Approver
	04-Dec-2014 06:58:00 PM	Approver
	04-Dec-2014 09:15:39 PM	Approver
	04-Dec-2014 09:41:49 PM	Approver
	05-Dec-2014 11:07:06 PM	Author