1.0 Title Page

Statistical Analysis Plan

Study 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

Date: 13 Nov 2017

Version 1.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Clinical Statistics Department for Study M14-347.

It provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

This analysis plan describes the primary and secondary efficacy analyses as well as the safety analysis of data except pharmacokinetic, serological and mRNA biomarkers which will be analyzed separately. It takes into account ICH Guidelines E3 and E9.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 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.

4.2 Design Diagram

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. 252 adult subjects who participated and successfully completed Study M14-115 Induction were enrolled into this study.

Subjects were 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 was anticipated to be up to

40 weeks. There was a ± 3-day window for all study visits. An effort was made to bring the subject back to their original study visit (calculated from Week 0) if they were out of the visit window.

Study visits for clinical and safety assessments were performed at Weeks 0, 8, 16, 24, 32 and 40/Premature Discontinuation (PD). All subjects were provided with a paper subject diary in which they could record CD-related symptoms (number of liquid or very soft stools, abdominal pain rating, and general well-being) and adalimumab dosing information throughout the study. Blood samples were 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 were collected. The stool samples were taken before starting bowel preparations for endoscopy. Endoscopic evaluation were performed at Week 40/PD, if the PD occurred after Week 24. CDAI evaluations were calculated based on entries recorded into the subject's diary at all study visits. The SFPS (Stool [liquid/soft] Frequency + Abdominal Pain Score) were calculated using the weighted values for the CDAI components "Number of liquid or very soft stools" and "Abdominal pain."

All subjects received open-label adalimumab 40 mg every other week (eow) beginning at Week 0. No dose was administered at Week 40. Subjects might be escalated to adalimumab 40 mg every week (ew) at or after Week 1 should the subject met the criteria for inadequate response (Table 1).

Table 1. Inadequate Response

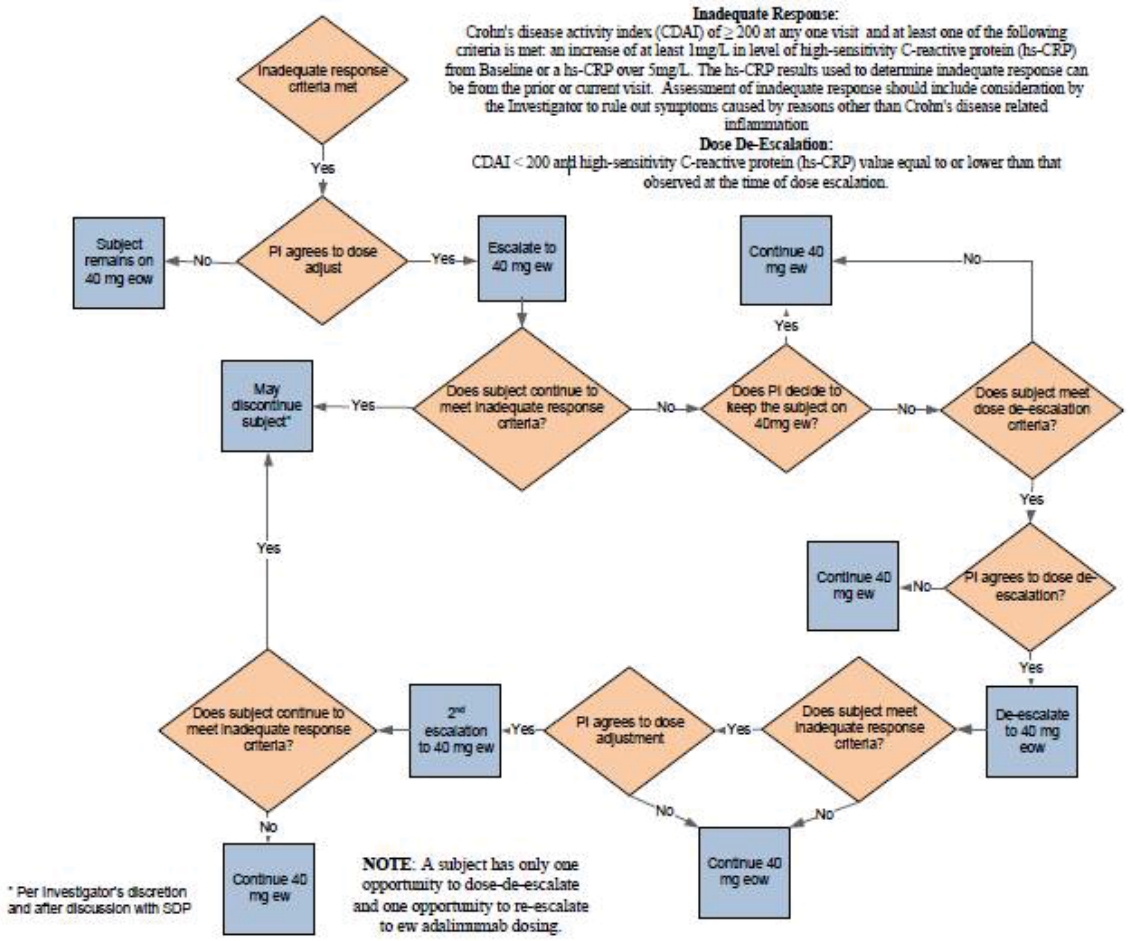
Response Type	Definition
Inadequate response	Crohn's disease activity index (CDAI) of ≥ 200 at any one visit and at least one of the following criteria is met: an increase of at least 1 mg/L in level of high-sensitivity C-reactive protein (hs-CRP) from Baseline or an hs-CRP ≥ 5 mg/L. The hs-CRP results 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 was considered in lieu of increases in steroid dose. Subjects who continued to experience inadequate response on 40 mg ew who were taking corticosteroids at Baseline of Study M14-115 might have their steroid dose increased, per the Investigator's discretion, in order to manage the subject's symptoms. Any subject who continued to experience inadequate response on 40 mg ew might 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, had one opportunity to de-escalate adalimumab dose to 40 mg eow provided the following criteria had 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 experienced inadequate response after dose de-escalation (using the same criteria outlined above), might again be escalated to 40 mg ew. A subject had only one opportunity to dose de-escalate and one opportunity to re-escalate to ew adalimumab dosing.

Changes in adalimumab dosing might only occur when the above criteria were met but were not mandatory. A schematic for dose adjustments is presented in Figure 1.

Figure 1. Dose Adjustment Algorithm



Subjects might discontinue adalimumab treatment at any time during study participation (Section 5.4). Subjects would be discontinued from the study if they withdraw consent or if they were deemed unsuitable to continue for any reason by the Investigator. Subjects who ended study participation early would have a PD visit. All subjects were to 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 would not be required for any subject who initiated commercial adalimumab.

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

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

- Immunosuppressant doses might be decreased or terminated in the event of moderate-to-severe treatment-related toxicities.
- Subjects who were 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 might be undertaken at the Investigator's discretion in subjects who were receiving adalimumab 40 mg ew.

  For subjects taking adalimumab 40 mg eow, adalimumab dose escalation (for subjects who meet inadequate response criteria) were to be considered in lieu of increases in the steroid dose.

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 Call1
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		
Crohn's Disease Activity Index (CDAI)	X[a]	X	X	X	X	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 Call1
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	
Chest X-Ray (for patients in Ukraine only)[n]				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.

n. For patients in Ukraine only. Chest x-ray should be performed up to two weeks prior to the Week 24 visit, as a screening measure for newly developed/reactivated TB. In case diagnosis of TB is established following further assessments, such patients should be immediately discontinued from the study (as a consequence of diagnosis of TB). Procedures as per Section 5.4.1 "Discontinuation of Individual Subjects" should be applied in such cases.

4.3 Sample Size

No sample was calculated for this study.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

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

Intent-to-Treat Analysis Set

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

Safety Analysis Set

The Safety analysis set will include all subjects who receive at least one injection of study drug during the study.

For analysis purpose, these two populations are same.

5.2 Variables Used for Stratification of Randomization

There is no randomization for this open-label study.

6.0 Analysis Conventions

Definition of Week 0

The Week 0 visit date is the date when the first dose of Study M14-347 study drug is received and referred to as Day 1 or Week 0. The Week 0 value for a variable is defined as the last non-missing value on or before the date of the first dose of Study M14-347 study drug.

Definition of Rx Days (Days Relative to the First Dose of Study Drug)

The Rx Day is calculated as the event date minus the date of first dose of study drug plus 1 when the time point of interest is after the date of first dose of study drug, or the event date minus the date of first dose of study drug when the time point of interest is prior to the date of first dose of study drug. It provides a quantitative measure of days between the time point of interest and the first dose date. The day of the first dose of study drug is defined as Rx Day 1, while the day prior to the first study drug dose is defined as Rx Day –1 (there is no Rx Day 0).

Dealing with Multiple Measurements Collected on the Same Day

For efficacy related analyses, if multiple measurements for a particular parameter are collected on the same day for the same subject, the average of those measurements will be used.

For safety related analyses, if multiple measurements are made for a particular laboratory or vital sign parameter on the same day for the same subjects, the later time one will be used if there is time or the average of the values will be used in the analyses of change from Baseline. For summaries and listings for shift from baseline and potentially significant values, all collected values within the pre-specified treatment window will be used.

Definition of Analysis Windows

Since subjects do not always adhere to the study visit schedule, the following rules will be applied to assign actual visits to protocol-specified visits including early termination visits. For each study visit mentioned in the protocol, a nominal or target day will be selected to represent the corresponding visit along with a window around the target day. Windows will be selected in a non-overlapping fashion so that a date collected on the case report form (CRF) does not correspond to multiple visit windows. Moreover, windows will not discard any post-baseline measurement recorded on the CRF. If a subject had 2 or more actual visits in one visit window, the visit closest to the target will be used as

the study visit for that window. If two visits are equidistant from the target day, then the later visit will be used for reporting.

The visit windows and the nominal (target) day for each study visit are shown in the following tables.

Table 3. Visit Windows for Analysis of Efficacy Variables (Except IBDQ, EQ-5D, WPAI, and SES-CD), Laboratory Parameters, and Vital Signs

Protocol Specified Visit Week	Lower Bound	Nominal Day	Upper Bound
0	–999	1	1
8	2	57	85
16	86	113	141
24	142	169	197
32	198	225	253
40	254	281	309

Table 4. Visit Windows for Analysis of IBDQ, EQ-5D, WPAI, and Abdominal Pain Rating Scale

Protocol Specified Visit Week	Lower Bound	Nominal Day	Upper Bound
0	–999	1	1
16	2	113	169
32	170	225	253
40	254	281	309

Table 5. Visit Windows for SES-CD

Protocol Specified Visit Week	Lower Bound	Nominal Day	Upper Bound
0	–999	1	1
40	2	281	561

Note: If an endoscopy was done within 7 days after first dose of Study M14-347, the SES-CD will still be used as Study M14-347 Baseline value.

CD-Related Concomitant Therapy

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 will be censored for efficacy assessments (i.e., will be considered non-responders for categorical endpoints and will have Study M14-115 Baseline values 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.

The equivalent steroid dose will be determined based on the table below:

Corticosteroid	Equivalent Dose (mg)
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Triamcinolone	4.0
Methylprednisolone	4.0
Betamethasone	0.75
Dexamethasone	0.75
Budesonide	1
Beclomethasone	5
Beclometasone	5

If a subject met the censoring criteria for CD related concomitant therapy during Study M14-115, all binary efficacy endpoints will be No in Study M14-347, all observed values in Study M14-347 will be replaced by Study M14-115 Baseline values.

Dose Escalation

Subjects who had dose escalated to 40 mg ew will be censored for efficacy assessments (i.e., will be considered non-responders for categorical endpoints and will have

Study M14-115 Baseline values carried forward for non-categorical assessments) from that point through the end of the study.

Definition of Missing Data Imputation

Missing data imputation will be done only for efficacy variables (categorical and continuous variables). For the analysis other than efficacy, no imputation will be done for missing values.

Non-Responder Imputation (NRI)

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

Observed Case (OC)

Observed case analysis will be performed such that missing values will not be imputed. However, all observed values will be replaced by Study M14-115 Baseline value once subjects met the censoring criteria for CD-related concomitant therapy or dose escalation, whichever is earlier.

Last Observation Carried Forward (LOCF)

For all variables (categorical variables and continuous variables), the following rules will be used for the LOCF approach:

1. Baseline and Pre-Baseline values will not be used to impute the missing Post-Baseline values.
2. Missing values after Study Day 1 will be imputed using the latest non-missing values after Day 1 and prior to the missing value. If there are no non-missing values after Baseline, then the LOCF value will be missing.

Rule for CDAI Calculation

Up to 14 days of diary entries will be evaluated for the CDAI calculation for each visit. The diary entries on the days the subjects receive endoscopy preparation medications, the day of endoscopy procedure, and 2 days after endoscopy procedure will be excluded. For each CDAI subscore, the available scores from the most recent diary days (at least 4 days, up to 7 days) prior to actual day of the study visit will be summed, and then multiplied by the corresponding multiplier to get subtotal score. If available diary entries are fewer than 7 days, the subtotal score will be calculated as (summed total available score/number of days) × 7 × corresponding multiplier. The three subtotal scores (number of liquid/very soft stools, abdominal pain rating, and general well-being) will then be rounded to one decimal. The final CDAI is rounded to a whole number.

If a subject has less than 4 days of diary data, the total CDAI score will not be calculated and will be considered missing.

SFPS

SFPS is the CDAI components "Number of liquid or very soft stools" and "Abdominal pain" (Stool [liquid/soft] Frequency + Abdominal Pain Score). The sub-total score for each component is calculated as the sum of the 7 day diary score multiplied by the corresponding multiplier using the same rule for CDAI calculation.

If a subject has less than 4 days of diary data, the SFPS will not be calculated and will be considered missing.

SES-CD Scoring

All colonoscopies shall be performed and recorded in video format. Investigators shall provide their SES-CD assessment on the SES-CD sheet for the baseline and Week 40/Premature Discontinuation visits. The investigator SES-CD are to be entered in the appropriate eCRF, however neither the Investigator's Induction Baseline nor Week 40 SES-CD will be used for the study's efficacy analyses.

Two primary central reviewers will evaluate the videotaped colonoscopies separately and provide their SES-CD to Parexel. A third central reviewer will adjudicate between the two initial reviewers' SES-CD if there is discrepancy in any SES-CD variable. The adjudicator will select the final SES-CD that he/she most agrees with from those provided by the two primary reviewers, and this final SES-CD will be entered into the study database and be used for the study's efficacy analyses. If there is no discrepancy between the two primary central reviewers, that score will be entered into the study database and serve as the SES CD to be used for the study's efficacy analyses.

If there is a missing SES-CD individual variable in the SES-CD that serves as the SES-CD for the study's efficacy analyses, the following imputation rules will be applied:

The missing SES-CD individual variables at Study M14-115 Baseline will be imputed as 0. Study M14-115 Baseline SES-CD will be used to determine endoscopic improvement.

The missing SES-CD individual variables for Study M14-347 Week 0 or Study M14-347 Week 40 will be imputed as 0 if there are 8 or fewer missing individual variables. If more than 8 individual variables are missing, the total SES-CD will be missing for that visit.

Hs-CRP

From November 2014 to December 2015, Roche hs-CRP kit lot 604450 was in use at ICON. In December 2015 ICON altered the study team of a bias in the lot of the Roche Diagnostic C-creative protein high sensitive reagent. ICON then informed the study team of the extent of the under recovery in March 2016. This lot was "retrospectively expired" as the low standard beads agglutinated causing specimen results that are below 5 mg/L to be up to 25% lower than the accurate value. ICON later determined with Roche that the affected samples were those tested from May 18, 2015 to December 2015.

In the Study M14-347 approximately 146 samples were affected according to ICON. AbbVie obtained the final listing of affected samples/results from ICON on August 10, 2016. A correction factor developed by Roche and ICON will be applied to

all affected specimens with a concentration between 0.51 to 4.99 mg/L and will replace the initially provided hs-CRP values in the study database.

For Study M14-347, both Roche and Abbott platform are used to measure hs-CRP. The study team has decided to use Abbott platform for CSR analysis. If hs-CRP was measured by Roche platform only, the value will be converted to Abbott equivalent by a conversion factor.

Definition of Endoscopic Improvement

SES-CD ≤ 4 and at least two point reduction from Study M14-115 Baseline and no subscore > 1 in any individual variable.

Definition of CDAI Remission

CDAI < 150

Definition of SFPS Remission

SFPS < 50

Definition of CDAI Response

Decrease in CDAI ≥ 70 points from Study M14-115 Baseline

Definition of Enhanced CDAI Response

Decrease in CDAI ≥ 100 points from Study M14-115 Baseline

Definition of Endoscopic Response

Decrease in SES-CD > 50% from Study M14-115 Baseline

Definition of IBDQ Response

Increase in IBDQ ≥ 16 from Study M14-115 Baseline

Definition of IBDQ Remission

IBDQ ≥ 170

Definition of Symptomatic Remission

Average daily stool frequency ≤ 1.5 and not worse than Study M14-115 Induction baseline AND average daily abdominal pain ≤ 1.0 and not worse than Study M14-115 Induction baseline.

Definition of Symptomatic Response

Average daily stool frequency at least 30% reduction from Study M14-115 Induction baseline and average daily abdominal pain not worse than Study M14-115 Induction baseline OR average daily abdominal pain at least 30% reduction from Study M14-115 Induction baseline and average daily stool frequency not worse than Study M14-115 Induction baseline.

Discontinued Corticosteroid Use at Each Visit Among Subjects Who Used Corticosteroids at Week 0 of Study M14-347

Discontinued steroid use at each visit is based on the steroid use on the date of CDAI measurement for that visit. If the subject has no CDAI for the visit, the steroid use on the nominal day for that visit (Table 3) will be evaluated.

If a subject discontinued the study, 'discontinued corticosteroid use' will be classified as No from that point through the end of the study.

If a subject met censoring criteria for CD-related concomitant therapy or dose escalation, whichever is earlier, 'discontinued steroid use' will be classified as No from that point through the end of the study.

EuroQol-5D-5L (EQ-5D)

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.

The EQ-5D consists of 2 pages. The first page measures 5 dimensions of the health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels per dimension (no problems, slight problems, moderate problems, severe problems, and unable corresponding to Level 1 to Level 5 respectively). The second page is an EQ Visual Analogue Scale (EQ VAS). EQ-5D health states, defined by the EQ-5D-5L descriptive system on the first page, may be converted into a single index value. The change from baseline of the index value and EQ VAS will be analyzed and reported. UK scoring algorithm will be used (Table 7).

Table 6. An EQ-5D-5L Value Set for England

	Central Estimate	Value for Health State 23245
Mobility		
No Problem	0	
Slight	0.051	0.051
Moderate	0.063	
Severe	0.212	
Unable	0.275	
Self-Care		
No Problem	0	
Slight	0.057	
Moderate	0.076	0.076
Severe	0.181	
Unable	0.217	
Usual Activities		
No Problem	0	
Slight	0.051	0.051
Moderate	0.067	
Severe	0.174	
Unable	0.190	
Pain/Discomfort		
No	0	
Slight	0.060	
Moderate	0.075	
Severe	0.276	0.276
Unable	0.341	
Anxiety/Depression		
Not	0	
Slight	0.079	
Moderate	0.104	
Severe	0.296	
Unable	0.301	0.301
The value for health state 23245: 1 – 0.9675 × (sum of the subscores)		**1 – 0.9675** × (0.051 + 0.076 + 0.051 + 0.276 + 0.301) = 0.270

The index value is 1 – 0.9675 × sum of 5 components based on central estimates.

The minimum index value is – 0.281 (health state 55555), and the maximum index value is 1 (health state 11111). (Reference: Devlin N, Shah KK, Feng Y, et al. Valuing health-related quality of life: an EQ-5D-5L value set for England. Health Econ. 2017.).

If one of the 5 dimensions is missing, the EQ-5D index value will be missing.

CD Related Hospitalizations and Major CD Related Events

CD related hospitalizations and major CD related events will be adjudicated according to the hospitalization adjudication charter.

6.1 Missing Dates Imputation

For Baseline, efficacy, and safety parameters, if the day and/or month are missing, the following conventions will be used to impute the missing dates:

- 01 for missing start day
- End of month for missing end day
- January 1st for missing start month
- December 31st for missing end month

In case of partially missing AE start and stop dates, the dates will be imputed by comparing to first dose date of study medication so that the corresponding AEs will be made treatment-emergent whenever possible. If the start date of an AE is partially missing and the month is the same as the start date of a new therapy, the AE will be made treatment emergent to the new therapy.

In case of missing or partially missing study drug dosing dates, the dates will not be imputed and subjects will be treated as not receiving dose on that date.

6.2 Dealing with Multiple Measurements Collected on the Same Day

For efficacy related analyses other than imaging endpoints, if multiple measurements for a particular parameter are collected on the same day for the same subject, the average of those measurements will be used.

For safety related analyses, if multiple measurements are made for a particular laboratory or vital sign parameter on the same day for the same subjects, the average of the values will be used in the analyses of change from Baseline. For summaries and listings for shift from baseline and potentially significant values, all collected values within the pre-specified treatment window will be used.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

7.1 Demographic and Baseline Characteristics

The following demographic and Study M14-115 baseline characteristics will be summarized by treatment group.

Continuous Variables:

- Age (years)
- Body weight (kg)
- Height (cm)
- Body Mass Index (kg/m^2)
- Blood Pressure (systolic/diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (RPM)
- Temperature (°C)
- CDAI
- SFPS
- Total SES-CD
- Crohn's Disease Duration (years)
- IBDQ score
- WPAI and its components
- EQ-5D
- Abdominal Pain Rating Scale

- hs-CRP mg/L
- Fecal calprotectin µg/g

Categorical Variables:

The baseline used for the following categorical variables is defined as the baseline in Study M14-115.

- Sex (male, female)
- Race
- Ethnicity
- Age (≤ median, > median)
- Age (< 40, 40 to < 65, 65 to < 75, ≥ 75)
- Baseline fecal calprotectin (≤ median, > median)
- Baseline fecal calprotectin (≤ 250 µg/g, > 250 µg/g)
- hs-CRP at Baseline (< 10 and ≥ 10 mg/L)
- hs-CRP at Baseline (≤ median, > median)
- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- Crohn's disease severity (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 (≤ median, > median)
- Disease duration (≤ 3 years, > 3 years)
- Tobacco use (user, ex-user, never used, unknown)
- Alcohol use (drinker, ex-drinker, non-drinker, unknown)
- Region (US, ex-US)

- Study M14-115 induction dose (higher, standard) [will be performed after Study M14-115 database lock.]

Demographic and Baseline characteristics will be summarized with descriptive statistics for the ITT analysis set. The number of non-missing observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. The counts and percentages will be summarized for categorical variables.

7.2 Medical/Surgical History

Medical/Surgical history data will be summarized using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Prior and Concomitant Medications

The number and percent of subjects who received a prior or concomitant medication will be tabulated by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary in alphabetical order for prior and concomitant medications, respectively.

A prior medication is defined as any medication taken prior to the first dose of study drug of Study M14-115 and collected in the CRF. A concomitant medication is defined as any medication other than study drug that (1) was started prior to the first dose of study drug of Study M14-347 and continued to be taken after the first dose of study drug or (2) was started after the first dose of study drug, but was not started after the last dose of study drug. A particular medication may be classified as "prior" or "concomitant" or "both."

The prior and concomitant medications will be summarized for ITT analysis set.

Concomitant medications at baseline include prior medications that have a start date before first dose of study drug and are ongoing or have a stop date after first dose of study drug.

The number and percent of subjects using Crohn's disease specific medications (including corticosteroids [0, ≤ 10 mg, ≤ 20 mg, or ≤ 30 mg prednisone equivalents], aminosalicylates, immunomodulators [defined as azathioprine, mercaptopurine, or methotrexate], and antibiotics) prior to Study M14-115 Baseline, and at Study M14-115 Baseline will be tabulated. In addition, the number and percent of subjects using infliximab at any time prior to Study M14-115 Baseline will be tabulated.

8.0 Patient Disposition

The number of subjects will be tabulated by country, investigator site and overall for the following sets:

- ITT analysis set
- Safety analysis set
- Subjects who completed study
- Subjects who prematurely discontinued study drug

In addition, the number and percentage of subjects who discontinued study drug will be summarized by primary reason and by any reason as recorded on the eCRF:

- Adverse event (AE)
- Withdrew consent
- Lost to follow-up
- Lack of efficacy
- Requires alternative (or prohibited) therapy
- Subject non-compliance
- Other

Subjects may have more than one reason for discontinuing study drug, but they will be counted once for the total number of discontinuations. Subjects have only one primary reason for discontinuing study drug or discontinuing from the study.

9.0 Study Drug Exposure and Compliance

9.1 Study Drug Exposure

The duration of exposure to study drug will be summarized using the mean, standard deviation, minimum, median, and maximum for the safety population. Duration of exposure is defined for each subject as number of days since first dose of study drug through the last study drug dose date + 70 days. Study drug dose date refers to recorded dates of injections of study drug.

9.2 Study Drug Compliance

The treatment compliance (%) of study drug will be summarized using the mean, standard deviation, minimum, median, and maximum for safety population. The compliance rate will be calculated as follows:

Compliance rate (%) = the total number of injection received/the total number of injection expected * 100

10.0 Efficacy Analysis

10.1 General Considerations

For all efficacy endpoints, the descriptive statistics including number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and number and percent for discrete variables, will be summarized for ITT analysis set. No statistical tests will be performed.

10.2 Primary Efficacy Analyses

The primary efficacy variable is the proportion of subjects with endoscopic improvement at Week 40 among subjects with endoscopic improvement at Week 0 of Study M14-347.

A two-sided 95% confidence interval will be calculated for ITT analysis set. Missing SES-CD at Week 40 will be imputed using non-responder imputation (NRI) approach. The LOCF method will be used as the sensitivity analyses.

10.3 Additional Efficacy Analyses

For additional efficacy endpoints, the baseline is defined as the Baseline in Study M14-115. The additional efficacy variables are listed as below.

- Proportion of subjects with CDAI remission (CDAI < 150) over time among subjects with CDAI remission at Week 0 of Study M14-347.
- Proportion of subjects with endoscopic improvement, defined as an SES-CD ≤ 4 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 40.
- Proportion of subjects with CDAI remission (CDAI < 150) over time.
- Proportion of subjects with CDAI < 150 at Week 40 and SES-CD ≤ 4 and at least a 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 40 among subjects with CDAI < 150 at Week 0 and SES-CD ≤ 4 and at least a 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 0 of Study M14-347.
- Proportion of subjects with CDAI < 150 at Week 40 and SES-CD ≤ 4 and at least a 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 40.
- Proportion of subjects with endoscopic response at Week 40 among subjects with endoscopic response at Week 0 of Study M14-347.
- Proportion of subjects with endoscopic response at Week 40.
- Change from Study M14-115 Baseline in fecal calprotectin level over time.

- Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 μg/g over time among subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 μg/g at Week 0 of Study M14-347.
- 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 among subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 μg/g at Week 0 of Study M14-347.
- 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 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 40 among subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 0 of Study M14-347.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 μg/g at Week 40.
- Proportion of subjects with SES-CD ≤ 2 at Week 40 among subjects with SESCD ≤ 2 at Week 0 of Study M14-347.
- Proportion of subjects with SES-CD ≤ 2 at Week 40.
- Proportion of subjects with CDAI response (decrease in CDAI ≥ 70 points from Study M14-115 Baseline) over time among subjects with CDAI response at Week 0 of Study M14-347.
- Proportion of subjects with CDAI response (decrease in CDAI ≥ 70 points from Study M14-115 Baseline) over time.
- Proportion of subjects with enhanced CDAI response (decrease in CDAI ≥ 100 points from Study M14-115 Baseline) over time among subjects with enhanced CDAI response at Week 0 of Study M14-347.

- Proportion of subjects with enhanced CDAI response (decrease in CDAI ≥ 100 points from Study M14-115 Baseline) over time.
- Change in IBDQ from Study M14-115 Baseline over time.
- Proportion of subjects who discontinue corticosteroid use at each visit among subjects who used corticosteroids at Week 0 of Study M14-347.
- Proportion of subjects who achieve CDAI remission and discontinue corticosteroid use at each visit among subjects who used corticosteroids at Week 0 of Study M14-347.
- Proportion of subjects with a SFPS remission (SFPS < 50) over time among subjects with SFPS remission at Week 0 of Study M14-347.
- Proportion of subjects with a SFPS remission (SFPS < 50) over time.
- Proportion of subjects with a SFPS remission (SFPS < 50) over time among subjects with SFPS ≥ 100 at Week 0 of Study M14-347.
- Proportion of subjects with SES-CD ≤ 3 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 40 among subjects with SES-CD ≤ 3 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 0 of Study M14-347.
- Proportion of subjects with SES-CD ≤ 3 and at least 2 point reduction versus Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 40
- Proportion of subjects with SES-CD = 0 at Week 40 among subjects with SESCD = 0 at Week 0 of Study M14-347.
- Proportion of subjects with SES-CD = 0 at Week 40.
- Proportion of subjects with a decrease of SES-CD ≥ 3 points from Study M14-115 Baseline at Week 40 among subjects with a decrease of SES-CD ≥ 3 points from Study M14-115 Baseline at Week 0 of Study M14-347.
- Proportion of subjects with a decrease of SES-CD ≥ 3 points from Study M14-115 Baseline at Week 40.
- Proportion of subjects with a decrease in SES-CD > 50% from Study M14-115 Baseline (or for subjects with an SES-CD of 4 at Study M14-115 Baseline, at least a 2-point reduction from Study M14-115 Baseline) at Week 40 among

subjects with a decrease in SES-CD > 50% from Study M14-115 Baseline (or for subjects with an SES-CD of 4 at Study M14-115 Baseline, at least a 2-point reduction from Study M14-115 Baseline) at Week 0 of Study M14-347.

- Proportion of subjects with a decrease in SES-CD > 50% from Study M14-115 Baseline (or for subjects with an SES-CD of 4 at Study M14-115 Baseline, at least a 2-point reduction from Study M14-115 Baseline) at Week 40.
- Change from Study M14-115 Baseline in hs-CRP level over time.
- Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Study M14-115 Baseline) over time among subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Study M14-115 Baseline) at Week 0 of Study M14-347.
- Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (decrease ≥ 16 points from Study M14-115 Baseline) over time.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) over time among subjects with IBDQ remission (IBDQ ≥ 170 points) at Week 0 of Study M14-347.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) over time.
- Change in WPAI from Study M14-115 Baseline over time.
- Change in European Quality of Life 5 Dimensions (EQ-5D) from Study M14-115 Baseline over time.
- Change in CDAI from Study M14-115 Baseline over time.
- Change in SFPS from Study M14-115 Baseline over time.
- Change in Abdominal Pain Rating Scale score from Study M14-115 Baseline over time.
- 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 Study M14-115 Baseline over time.
- Time to first dose escalation.

- Proportion of subjects who require weekly dosing at Week 1 of Study M14-347.
- Proportion of subjects with major CD related event (e.g., hospitalization, bowel surgery, abscess drainage).
- Proportion of subjects with CD related hospitalization.
- Proportion of subjects with CD related surgery.
- Proportion of subjects requiring dose escalation to weekly dosing during this study.
- Proportion of subjects with no draining fistulas over time among subjects with draining fistula at Study M14-115 Baseline.
- 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 Study M14-115 Baseline.
- Resolution of extraintestinal manifestations over time.
- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 1.5 (and not worse than Study M14-115 Baseline) and average daily abdominal pain ≤ 1.0 (and not worse than Study M14-115 Baseline) over time among subjects with Study M14-115 Baseline average daily stool frequency ≥ 2.5 or average daily abdominal pain ≥ 2.0.
- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than Study M14-115 Baseline) and average daily abdominal pain ≤ 1.0 (and not worse than Study M14-115 Baseline) over time among subjects with Study M14-115 Baseline average daily stool frequency ≥ 4.0 or average daily abdominal pain ≥ 2.0.
- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from Study M14-115 Baseline and average daily abdominal pain not worse than Study M14-115 Baseline or average daily abdominal pain at least 30% reduction from Study M14-115 Baseline and average daily stool frequency not worse than Study M14-115 Baseline, over time.

For categorical additional efficacy endpoints, the two-sided 95% confidence interval for the proportions will be provided. The NRI method will be used for subjects with missing data at the time point evaluated. The LOCF method will also be used as the sensitivity analyses.

For continuous additional efficacy endpoints, change from Study M14-115 Baseline 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 estimated by the product limit method. The 95% CI for the median time-to-event will also be provided if applicable.

The time to first occurrence of event will be calculated as (first occurrence of event date or censoring date – date of first dose of the treatment during this study + 1). Subjects who did not experience the event prior to discontinue or complete the study will be censored at the date the last assessment was taken. For the endpoint of time to dose escalation, subjects without experiencing an event will be censored at the last available dose date.

10.4 Handling of Multiplicity

Not applicable.

10.5 Efficacy Subgroup Analysis

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 Study M14-115 Baseline.

- Sex (male, female)
- Age (≤ median, > median)
- Race (white, non-white)
- 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)
- Study M14-115 induction dose (higher, standard) [will be performed after Study M14-115 database lock.]

11.0 Safety Analysis

11.1 General Considerations

Laboratory data, AEs, and vital signs are the primary safety parameters in this study. All safety analyses will be performed for Safety population.

The continuous data will be summarized using descriptive statistics, including mean, standard deviation, and median for subjects who have both baseline and post-baseline values by visit. Categorical data will be summarized using frequencies and percentages. The number of non-missing values will also be given.

11.2 Analysis of Adverse Events

The adverse event (AE) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 20.0 or later. The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). Unless otherwise specified, the adverse event will be

summarized by system organ classes (SOCs) and preferred terms (PTs), and presented in the alphabetical order.

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAE) are defined as events that begin or worsen either on or after the first dose of the study medication and within 70 days after the last dose of the study drug.

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

11.2.2 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized for the following AE categories:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event that was rated as related (Reasonable Possibility) to study drug by the investigator
- Any treatment-emergent severe adverse event
- Any treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of study drug
- Any treatment-emergent adverse event leading to death
- Any treatment-emergent adverse event of special interest

11.2.2.1 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing TEAEs will be tabulated by SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in the alphabetical order within each SOC.

A subject who reports more than one AE in different SOCs will be counted only once in the overall total. A subject who reports two or more different PTs within the same SOC will be counted only once in the SOC total. Subjects reporting more than one AE for a given PT will be counted only once for that PT using the most extreme incident (i.e., most "severe" for the severity tables and most "related" for the relationship tables).

11.2.2.2 Adverse Events by Maximum Severity

TEAEs will also be summarized by maximum severity. If a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the most extreme severity – severe. In this case, the subject will be counted under the severe category.

11.2.2.3 Adverse Events by Maximum Relationship

TEAEs will also be summarized by maximum relationship as assessed by the investigator. If a subject has an AE with an unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same AE with a relationship assessment of "Reasonable Possibility. In this case, the subject will be counted under the "Reasonable Possibility" category.

11.2.2.4 Serious Adverse Events (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All pre- and post-treatment serious adverse events (TESAEs), deaths, and AEs leading to discontinuation of study drug will be listed. The number and percentage of subjects experiencing SAEs (including deaths) and AEs leading to discontinuation of study drug will be tabulated.

11.2.2.5 Frequent (≥ 5%) Adverse Events by Preferred Term in Decreasing Frequency

TEAEs occurring 5% or more of the subjects will be only summarized by PT in the decreasing frequency.

11.2.2.6 Reasonably Possibly Related Adverse Events by System Organ Class and Preferred Term

Reasonable Possibility TEAEs will be summarized by SOC and PT.

11.2.2.7 Reasonably Possibly Related Serious Adverse Events by System Organ Class and Preferred Term

Reasonable Possibility serious TEAEs will be summarized by SOC and PT.

11.2.2.8 Adverse Events of Special Interests

The following AEs of special interest will be summarized by number and percentage of subjects experiencing an AE of interest. The AEs of interest will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) for the following AE categories:

- Any Infections AE
- Any Serious Infection AE
- Any Legionella Infection AE
- Any Diverticulitis AE
- Any Opportunistic Infection AE (Excluding Oral Candidiasis and TB)

- Any Oral Candidiasis
- Any Tuberculosis AE
- Any Active Tuberculosis
- Any Latent Tuberculosis
- Any Parasitic Infection AE
- Any Reactivation of Hepatitis B
- Any Progressive Multifocal Leukoencephalopathy (PML) AE
- Any Malignancy AE
- Any Lymphoma AE
- Any Hepatosplenic T-Cell Lymphoma AE (HSTCL)
- Any Non-Melanoma Skin Cancer (NMSC) AE
- Any Melanoma AE
- Any Leukemia AE
- Any Other Malignant AE (Excluding NMSC, Melanoma, Lymphoma, HSTCL, and Leukemia)
- Any Allergic Reaction (Including Angioedema/Anaphylaxis)
- Any Lupus-Like Reactions and Systemic Lupus Erythematosus
- Any Vasculitis AE
- Any Cutaneous Vasculitis AE
- Any Non-Cutaneous Vasculitis AE
- Any Sarcoidosis AE
- Any Autoimmune Hepatitis
- Any Myocardial Infarction Related AE
- Any Cerebrovascular Accident Related AE
- Any Congestive Heart Failure Related AE
- Any Pulmonary Embolism Related AE
- Any Interstitial Lung Disease AE
- Any Intestinal Perforation AE
- Any Intestinal Stricture in CD

- Any Pancreatitis AE
- Any Stevens-Johnson Syndrome AE
- Any Erythema Multiforme Related AE
- Any Worsening/New Onset of Psoriasis
- Any Demyelinating Disorder
- Any Amyotrophic Lateral Sclerosis AE
- Any Reversible Posterior Leukoencephalopathy Syndrome (RPLS) AE
- Any Hematologic Disorders AE (Including Pancytopenia)
- Any Liver Failure and Other Liver Event AE (Except Gall Bladder Related Events)
- Any Humira Administration Related Medication Errors AE
- Any Injection Site Reaction AE
- Any AE Leading to Death
- Any AE Leading to Discontinuation of Study Drug
- Any Deaths

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

11.2.2.9 Adverse Events by 100 Patient Years

The event rates per 100 patient years of exposure to study drug will be presented for TEAE overviews and for TEAEs SOC and PT where the number of events will be used as the numerator.

$$\frac{Number\ of\ TEAEs}{Total\ Patient\ Years} \times 100$$

where total patient years is defined as the sum of the study drug exposure of all subjects, as defined in an earlier section, normalized by 365.25, and rounded to 1 decimal place.

11.2.2.10 Listing of Adverse Events

The following additional summaries of AEs will be prepared.

- Listing of Subjects with Treatment-Emergent Adverse Event of Special Interests
- Listing of Subjects with Pretreatment Serious Adverse Events
- Listing of Subjects with Treatment-Emergent Serious Adverse Events
- Listing of all adverse events that led to discontinuation of study drug
- Listing of all deaths

11.3 Analysis of Laboratory Data

The summary statistics, including Study M14-115 Baseline mean, the mean at each visit, mean change from baseline, standard deviation, and median will be presented.

Shift tables from Study M14-115 Baseline to minimum, maximum, and the final value according to the normal range will be provided for each hematology, clinical chemistry parameter and urinalysis parameter. The laboratory data will be categorized as low, normal, or high based on the normal ranges of the laboratory used in this study. The shift tables will tabulate the number and percentage of subjects with Baseline values below/within/above the normal range versus minimum, maximum, final values below/within/above the normal range.

For selected laboratory parameter with Common Toxicity Criteria (CTC) a listing of all subjects with any laboratory determinations meeting CTC Version 4.0 (or later) of Grade ≥ 3 will be provided. For each of these subjects, the whole course of the parameter will be listed. For subjects with laboratory values with CTC ≥ 3, all of the laboratory parameters for those subjects will be listed.

The liver-specific laboratory tests include the serum glutamic-pyruvic transaminase (SGPT/ALT), serum glutamic-oxaloacetic transaminase (SGOT/AST), alkaline

phosphatase, and total bilirubin. Each of these laboratory values will be categorized as follows:

- < 1.5 × ULN,
- ≥ 1.5 × ULN TO < 3 × ULN,
- ≥ 3 × ULN TO < 5 × ULN,
- ≥ 5 × ULN TO < 8 × ULN, and
- ≥ 8 × ULN,

where ULN is the upper normal limit.

Shift tables showing shift from Baseline to maximum and final values will be presented using these five categories.

A listing of potentially clinically significant liver function laboratory values will be provided. The listing will include all subjects who met any of the following 4 criteria:

- ALT ≥ 2.5 × ULN, or
- AST ≥ 2.5 × ULN, or
- Alkaline phosphatase ≥ 2.5 × ULN, or
- Total bilirubin ≥ 1.5 × ULN

11.4 Analysis of Vital Signs and Weight

Vital sign variables include sitting systolic blood pressure, sitting diastolic blood pressure and heart rate. The criteria for potentially clinically significant vital sign findings are presented in Table 8.

Table 7. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure (mmHg)	Value ≤ 90 mmHg and/or decrease ≥ 20 mmHg from Baseline
	Value ≥ 180 mmHg and/or increase ≥ 20 mmHg from Baseline
Diastolic blood pressure (mmHg)	Value ≤ 50 mmHg and/or decrease ≥ 15 mmHg from Baseline
	Value ≥ 100 mmHg and/or increase ≥ 15 mmHg from Baseline
Heart rate (bpm)	Value ≤ 50 bpm and/or decrease ≥ 15 bpm from Baseline
	Value ≥ 120 bpm and/or increase ≥ 15 bpm from Baseline

The summary statistics, including Study M14-115 Baseline mean, the mean at each visit, mean change from baseline, standard deviation, and median will be presented. The number and percentage of subjects meeting the criteria for potentially clinically significant (PCS) vital sign values will also be summarized.

Vital sign results meeting the criteria for PCS findings will be identified in a listing.

11.5 Analysis for Other Safety Variables

Not applicable for the current planned analysis.

11.6 Safety Subgroup Analysis

Not applicable.

12.0 Summary of Changes

12.1 Summary of Changes Between the Latest Version of Protocol and the Current SAP

The following efficacy variables are mentioned in the protocol but will not be summarized as they were removed from Study M14-115 protocol:

Proportion of subjects with predicted endoscopic improvement at Week 40, using the 3 definitions and equations.

Correlation between actual SES-CD and Predicted SES-CD:

In addition, change in Bristol Stool Scale score from Baseline over time will not be summarized as Bristol Stool Chart data in ePRO was not collected in Study M14-347.

The following efficacy variables are not mentioned in the protocol but are added to the SAP:

Proportion of subjects with CD related hospitalization: CD related hospitalization is a component of major CD related event.

Proportion of subjects with CD related surgery: CD related surgery is a component of major CD related event.

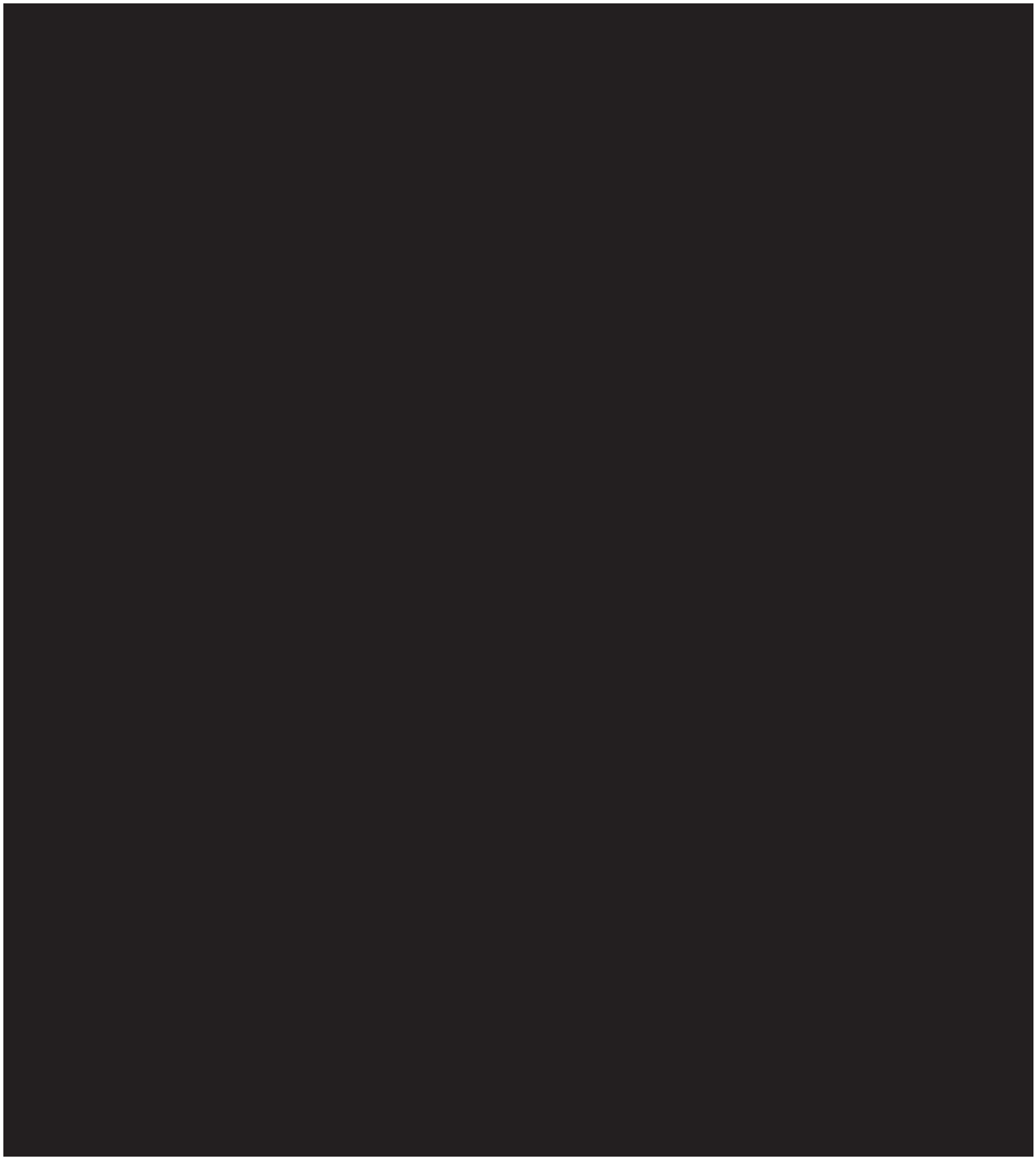
The following efficacy endpoints are added because they are used in new CD studies.

Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than Study M14-115 Baseline) and average daily abdominal pain ≤ 1.0 (and not worse than Study M14-115 Baseline) over time among subjects with Study M14-115 Baseline average daily stool frequency ≥ 4.0 or average daily abdominal pain ≥ 2.0: This endpoint is used for new CD studies as a primary efficacy endpoint.

Proportion of subjects with a decrease in SES-CD > 50% from Study M14-115 Baseline (or for subjects with an SES-CD of 4 at Study M14-115 Baseline, at least a 2-point reduction from Study M14-115 Baseline) at Week 40.

13.0 Appendix

13.1 Crohn's Disease Activity Index (CDAI)



[redacted]

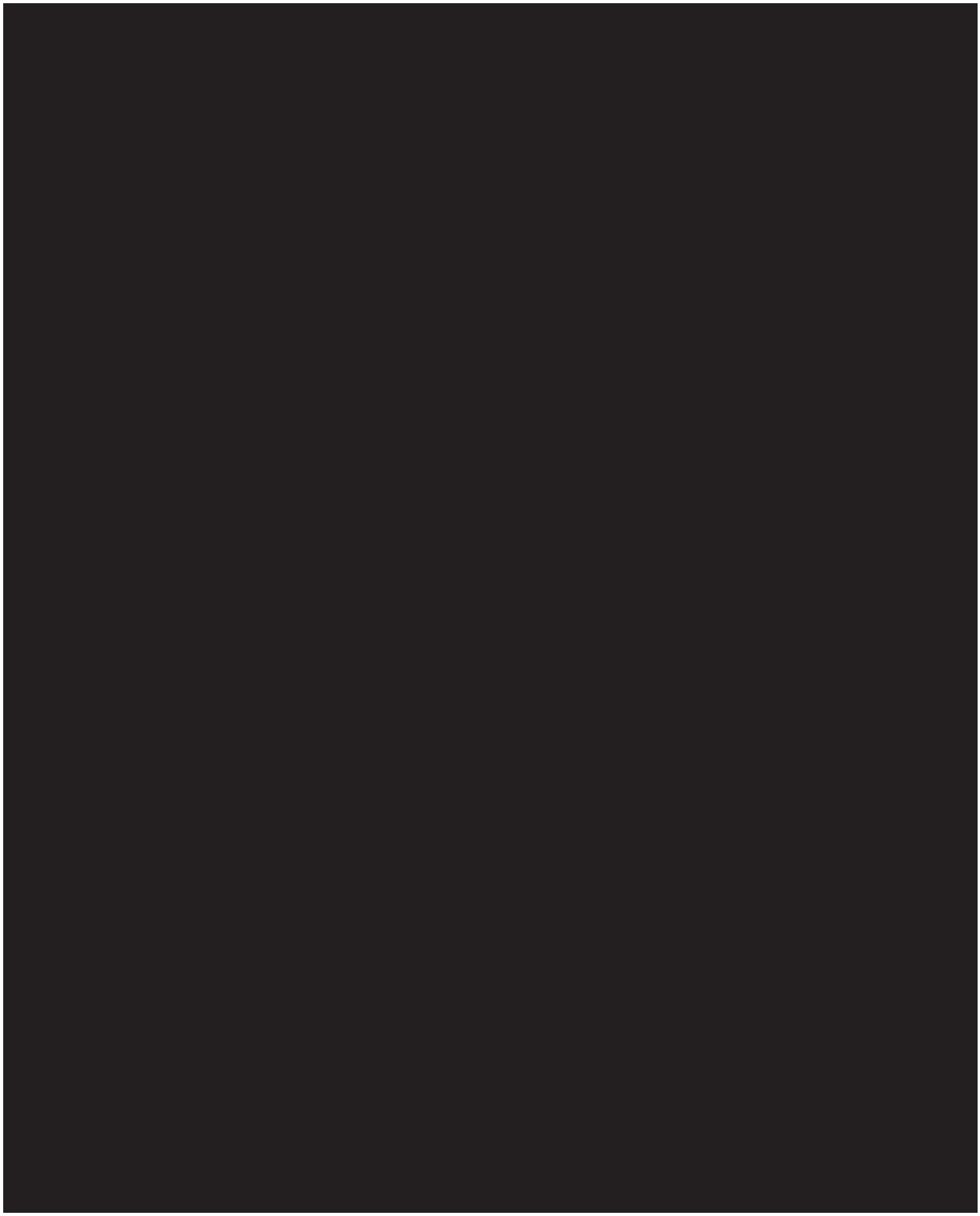
13.2 Simple Endoscopic Score – CD (SES-CD)

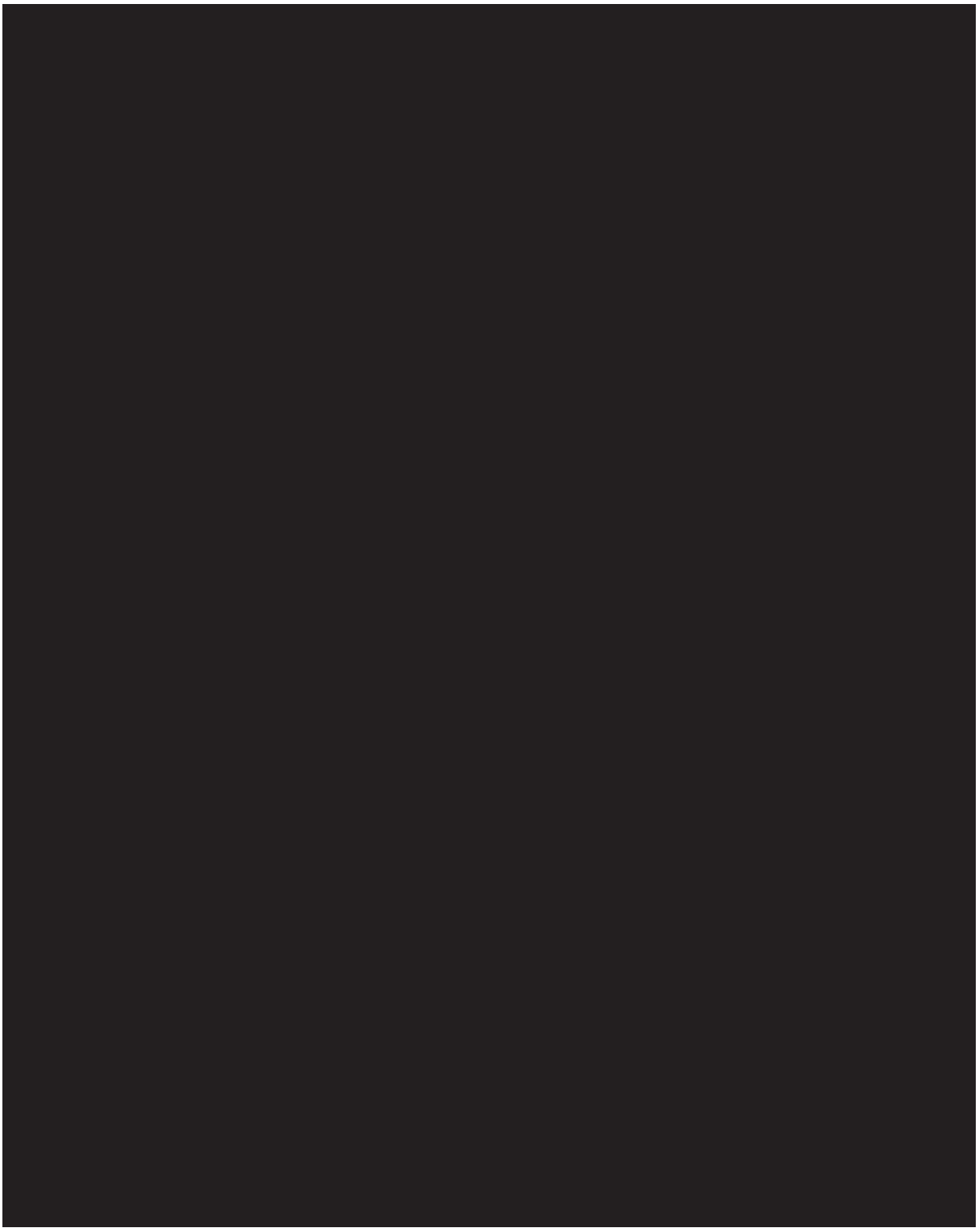
[redacted]

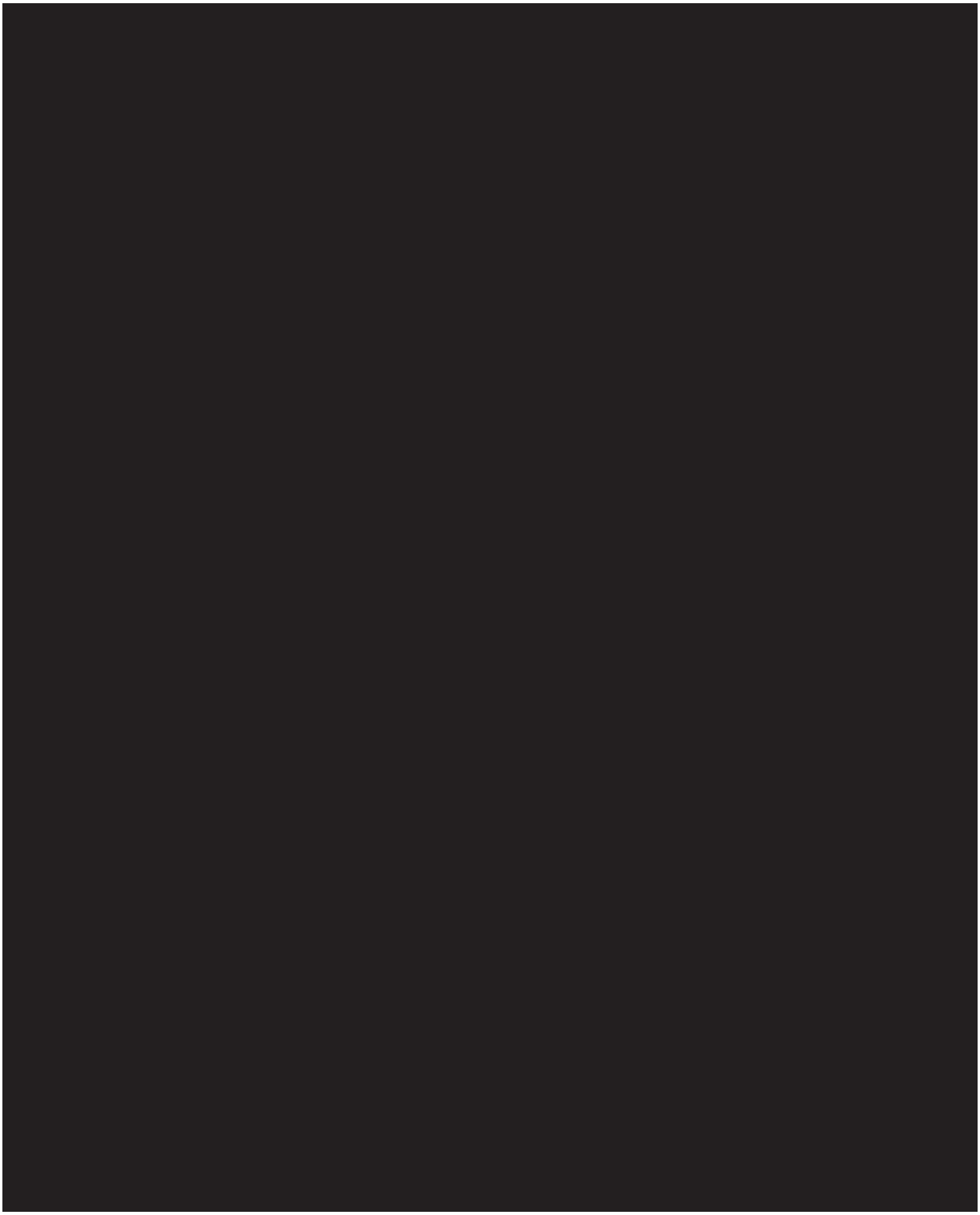
[redacted]

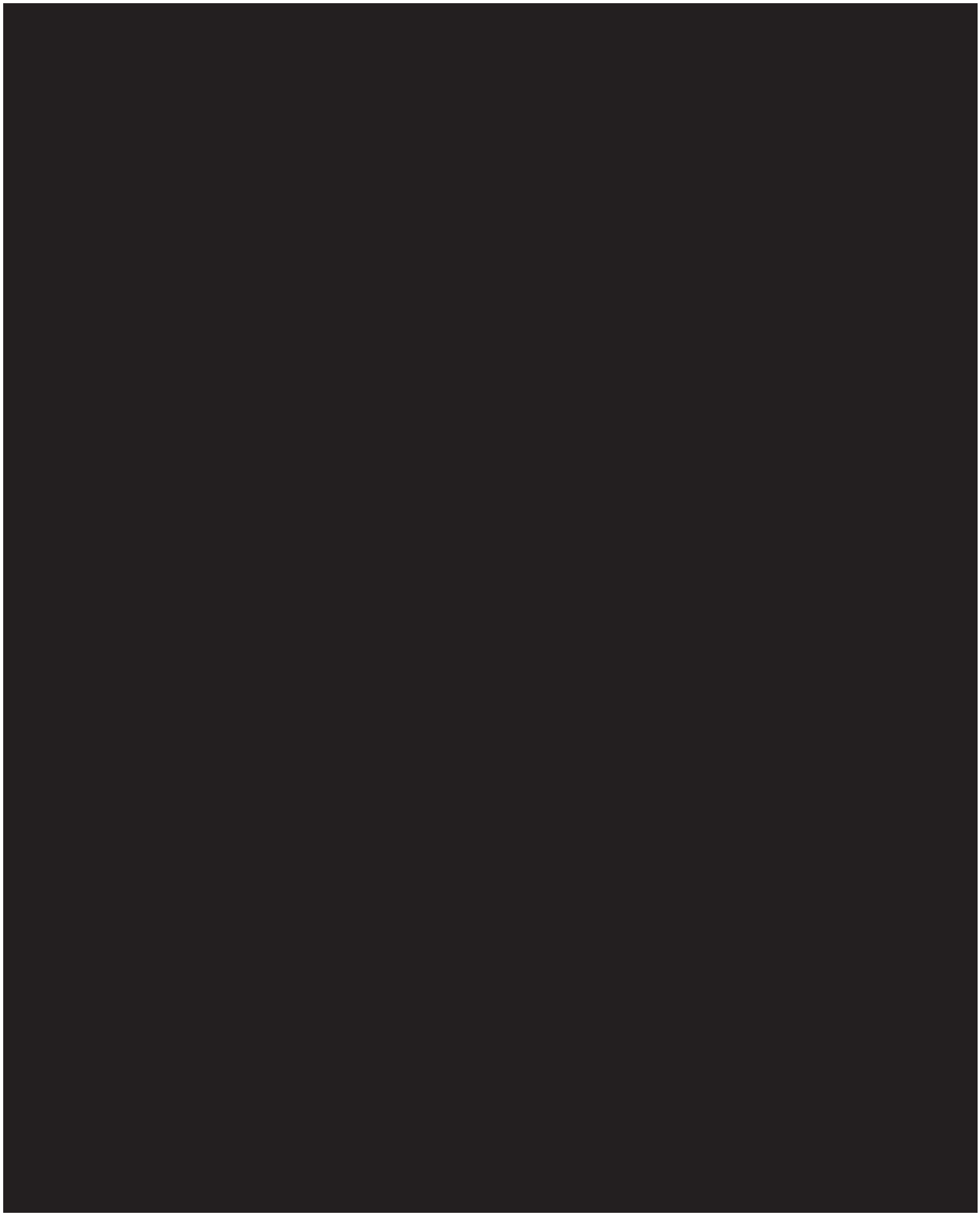
13.3 Inflammatory Bowel Disease Questionnaire (IBDQ)

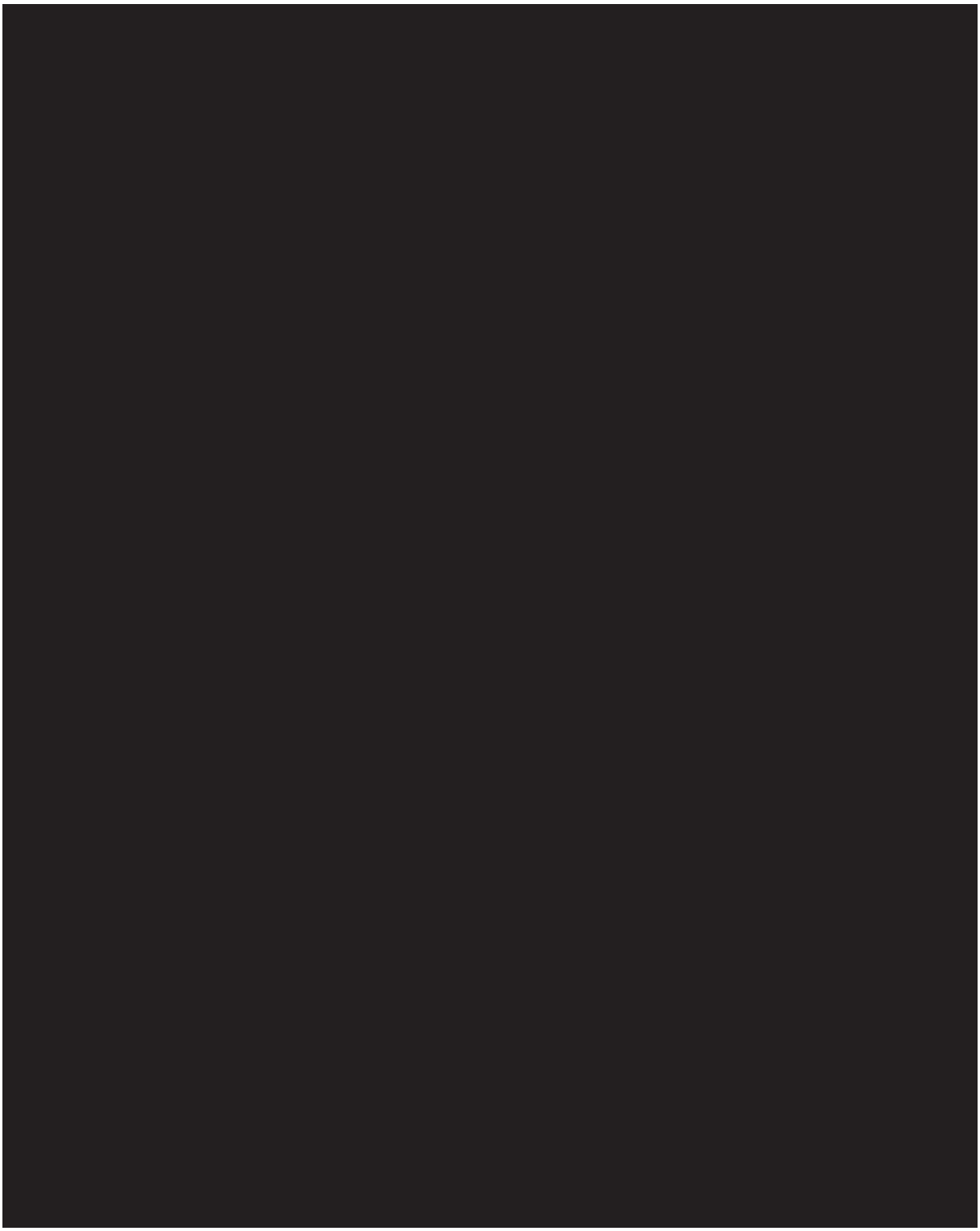
[redacted]

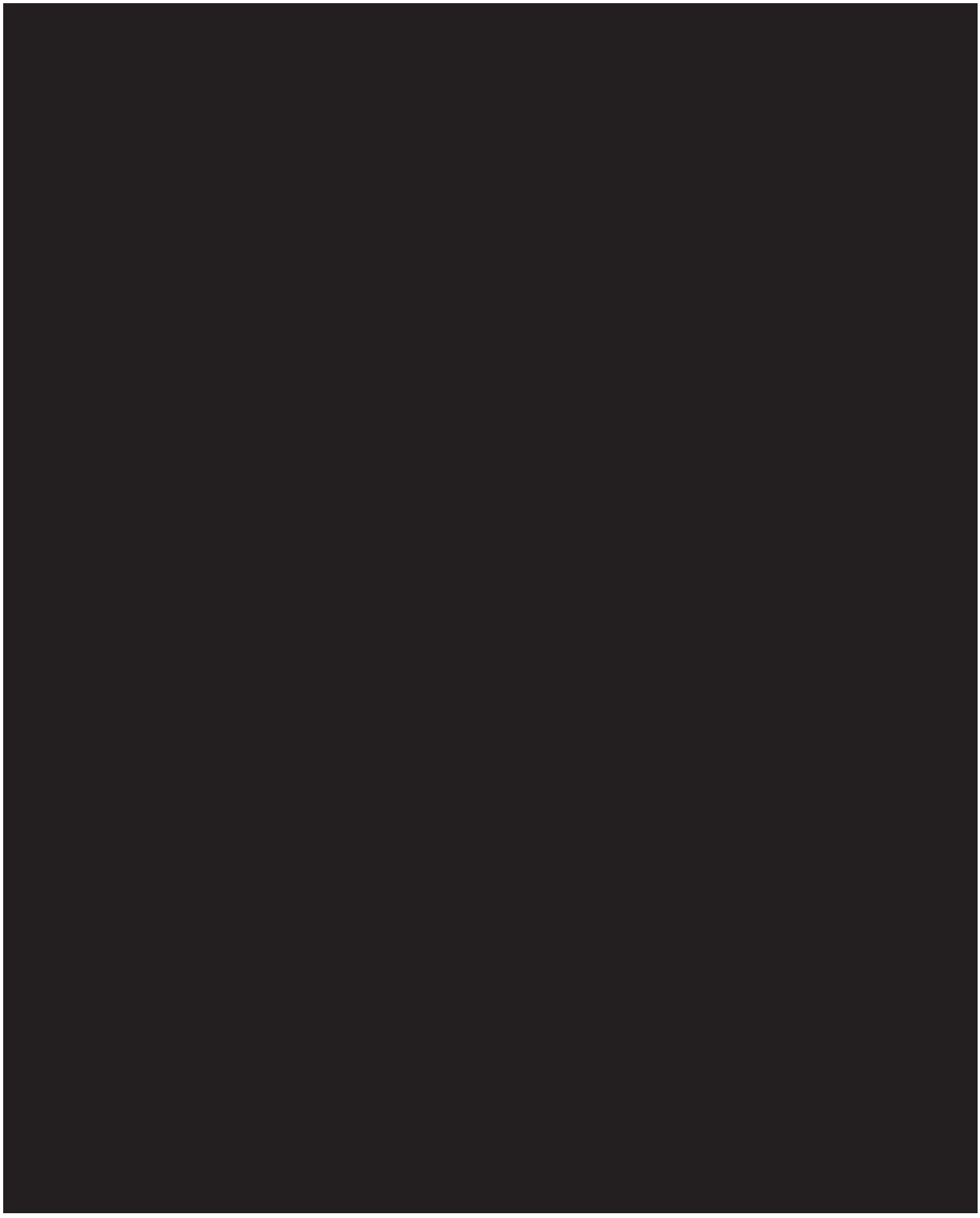


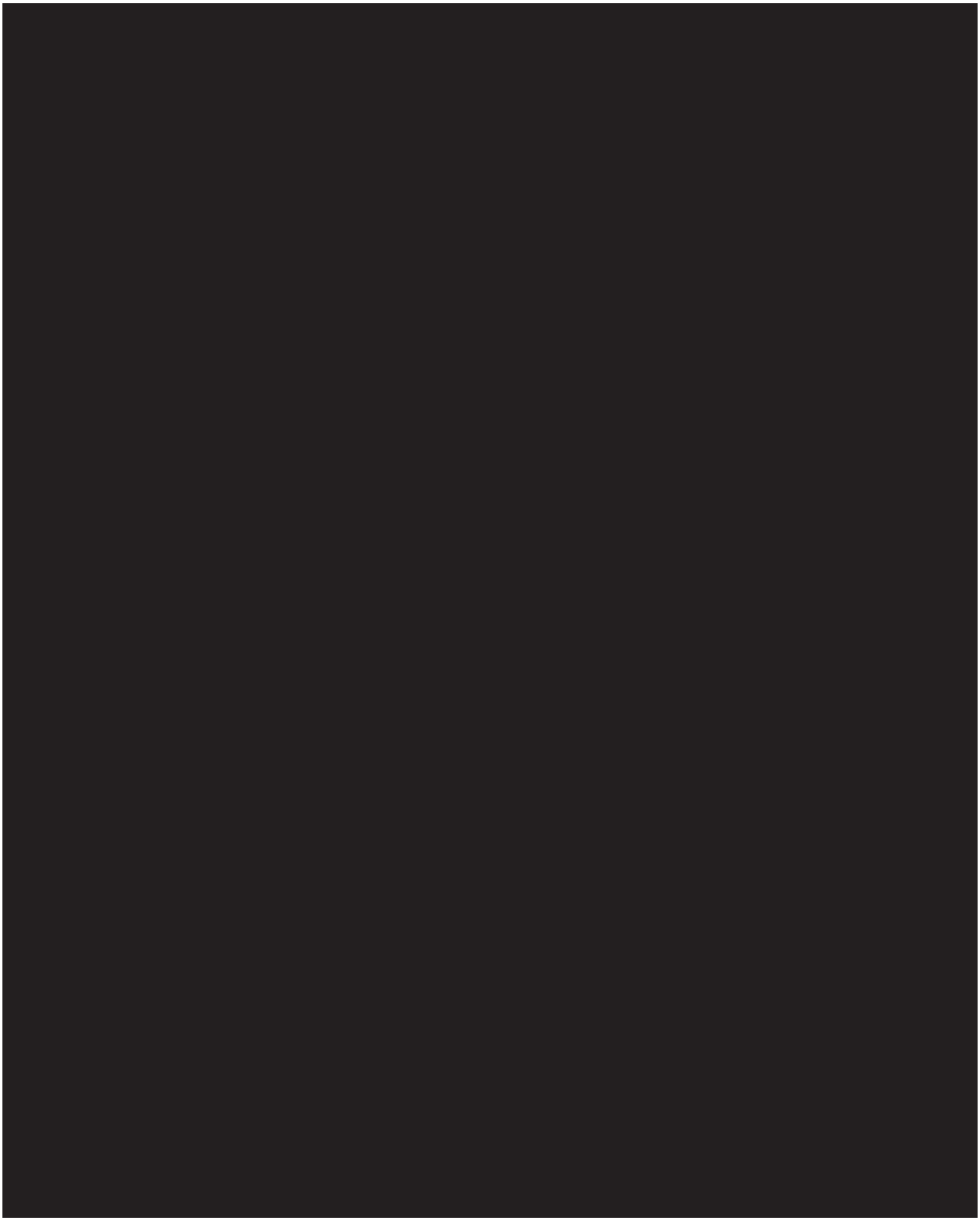


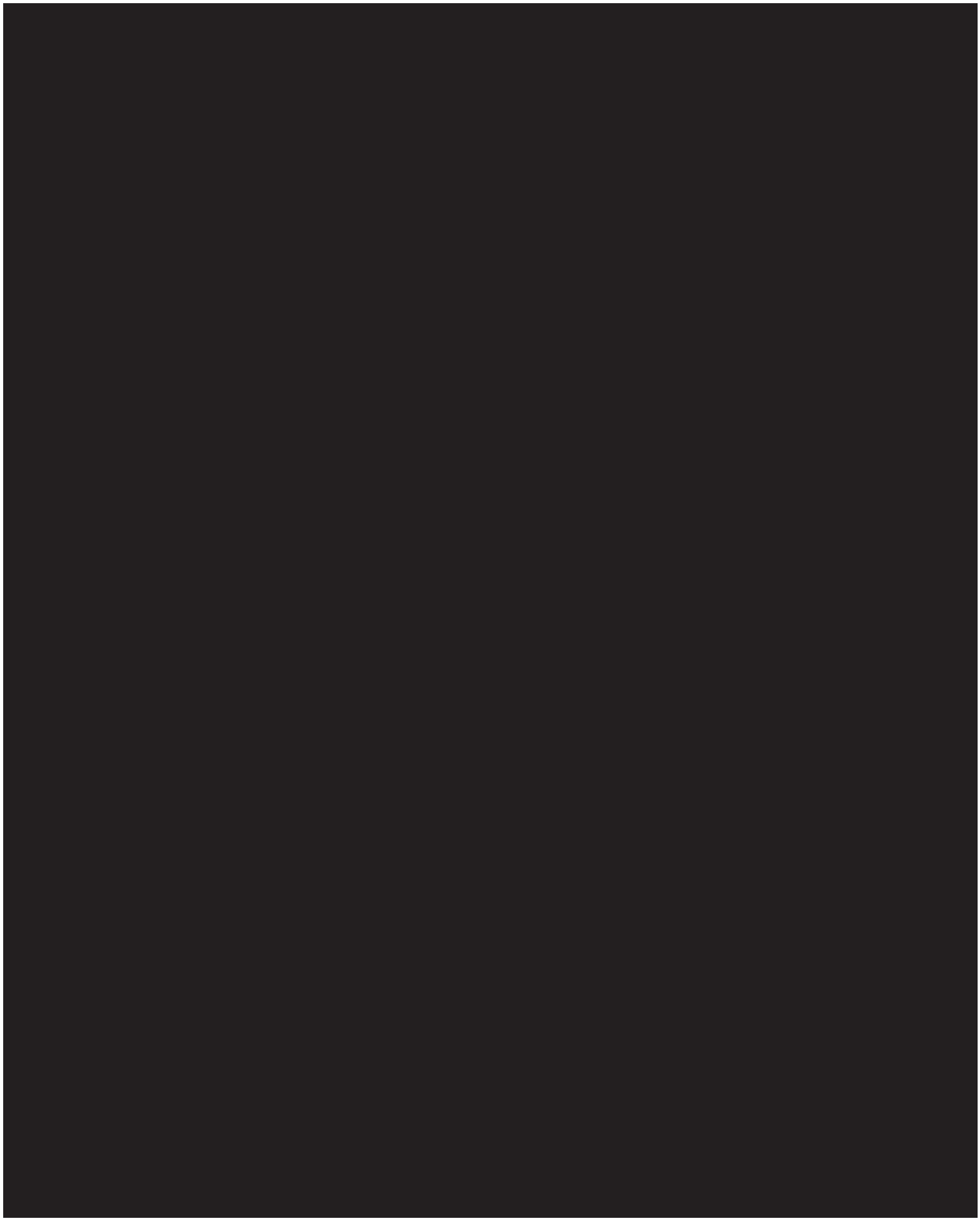


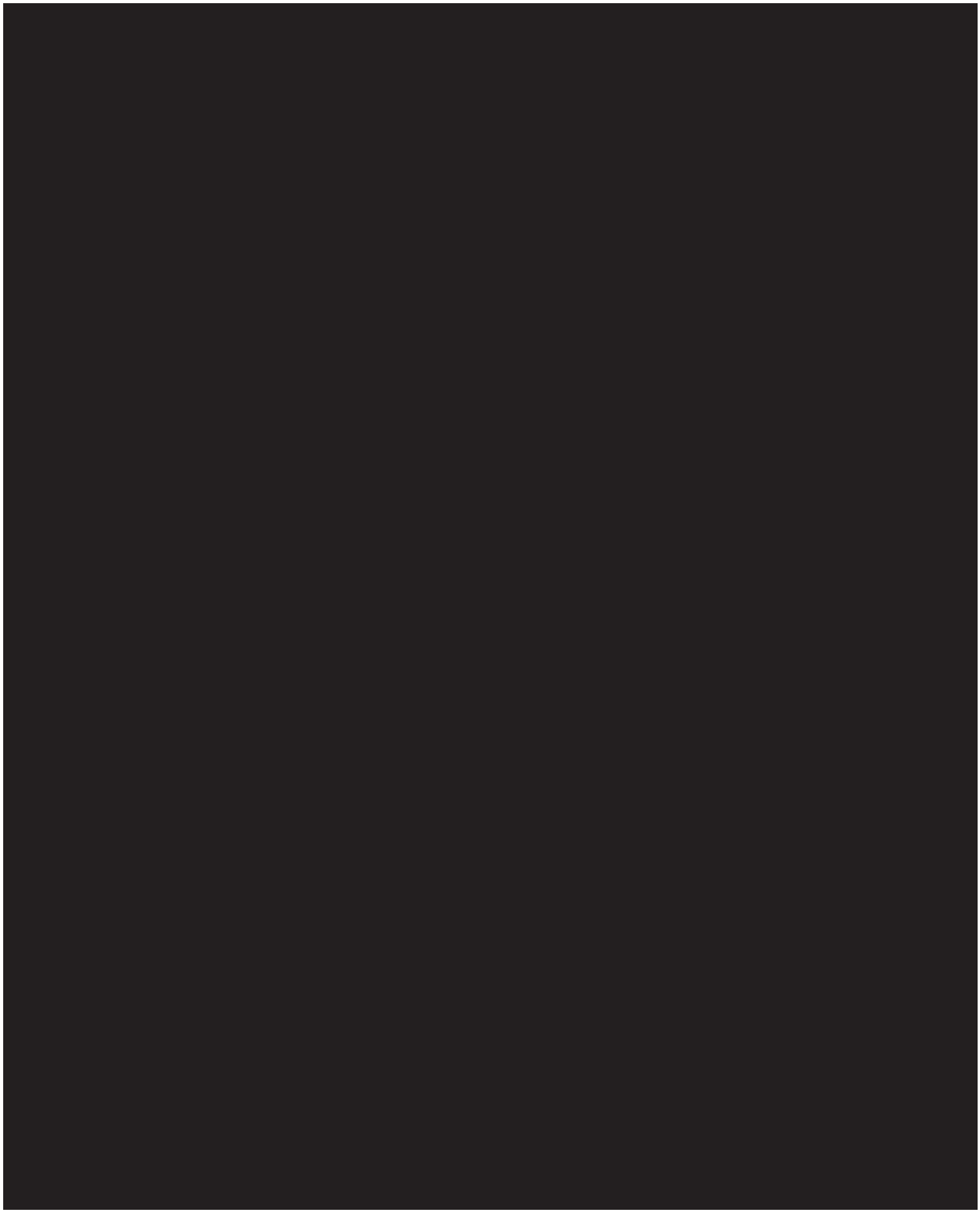






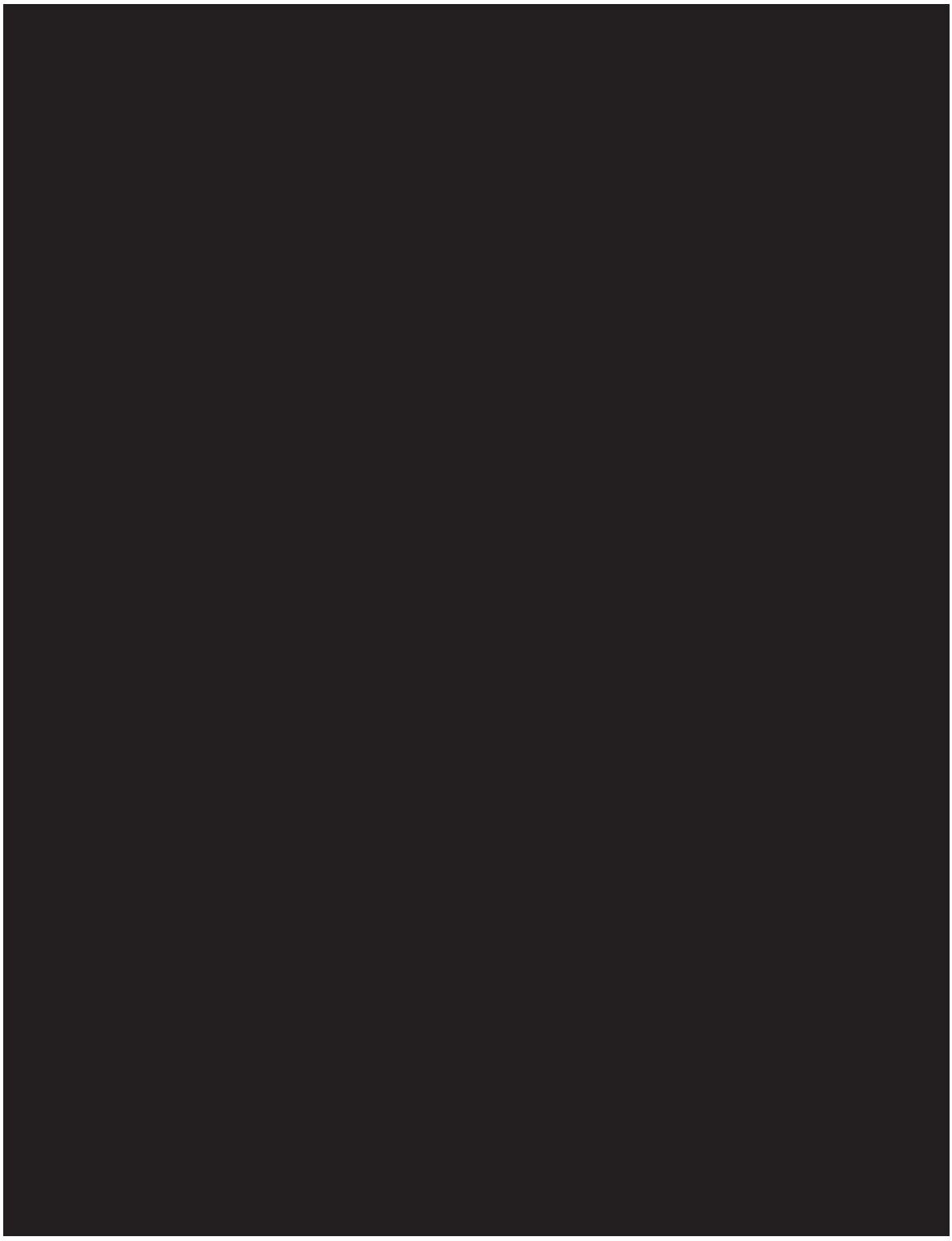




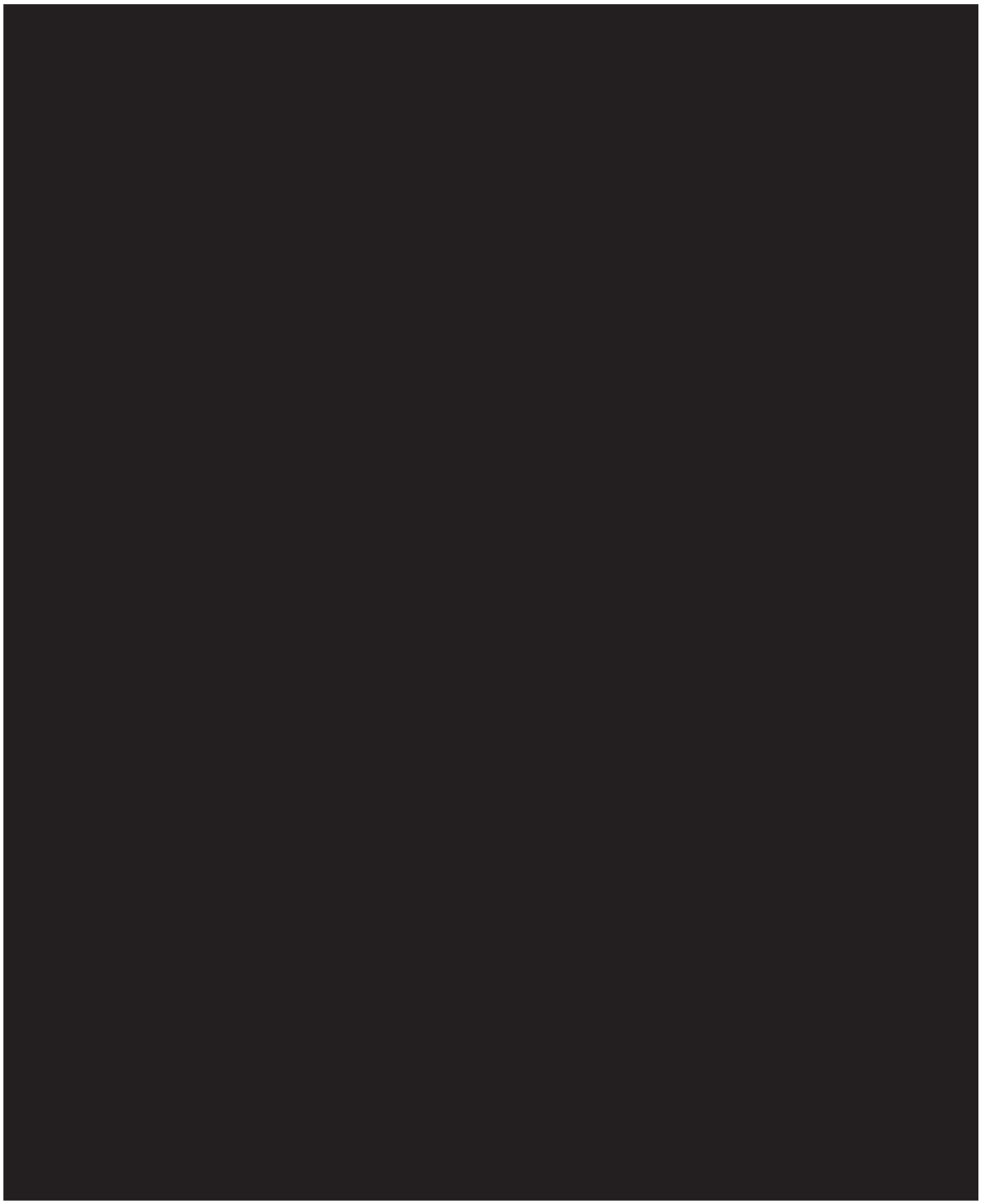


13.4 Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD)

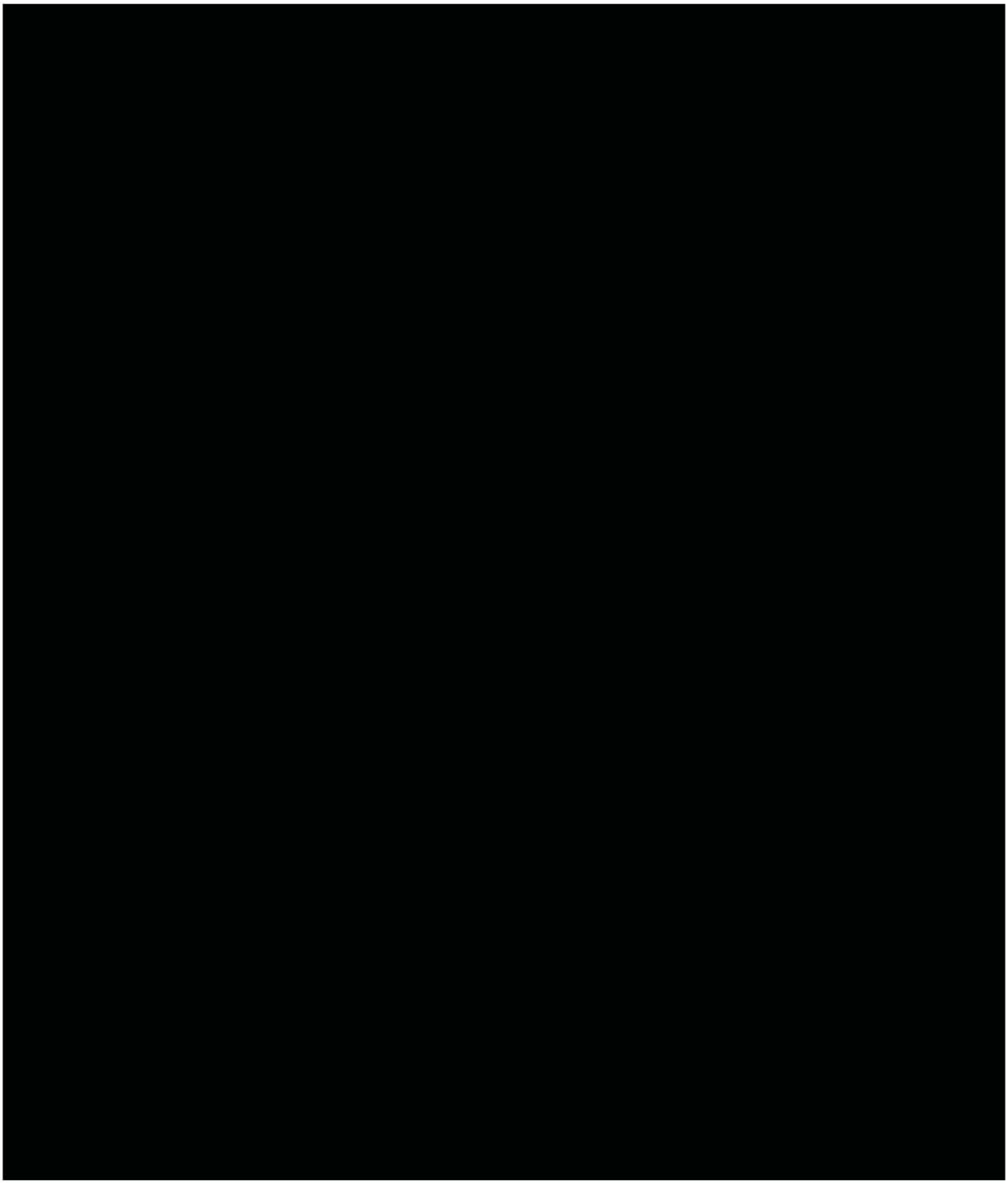
[redacted]



13.5 EQ-5D Questionnaires



13.6 Abdominal Pain Rating Scale



14.0 References

1. Devlin N, Shah KK, Feng Y, et al. Valuing health-related quality of life: an EQ-5D-5L value set for England. Health Econ. 2017.

Document Approval

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Signed by:	Date:	Meaning Of Signature:
[redacted]	[redacted]	**Author**
		Approver
		Author
		Approver