Title: A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients With Ulcerative Colitis and Crohn's Disease

NCT Number: NCT00790933

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STATISTICAL ANALYSIS PLAN

A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients With Ulcerative Colitis and Crohn's Disease

Protocol #: C13008

Amendment 10

SAP Version:
Amendment 2

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
5-ASAs	5-aminosalicylates
AEs	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CD	Crohn's disease
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CRP	C-reactive protein
CV	coefficient of variation
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQual
ET	early termination
GCP	good clinical practice
GI	gastrointestinal
h	hours
HAHA	human anti-human antibody
HBI	Harvey-Bradshaw Index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high level term
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN	interferon
IL	interleukin
IRB	institutional review board
IV	intravenous
JCV	JC virus, a neurotropic DNA polyomavirus
IVRS	interactive voice response system

Abbreviation	Term
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MCS	mental component score
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc. or its affiliates
MLN0002	Vedolizumab
NSAID	nonsteroidal anti-inflammatory drug
PCS	physical component score
PD	pharmacodynamics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PT	Preferred Term
PVC	polyvinylchloride
QOL	quality of life
RAMP	Risk Assessment and Minimization for PML
RBC	red blood cell(s)
SAEs	serious adverse events
SF-36	Short-Form 36
SOC	System Organ Class
TB	tuberculosis
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
UCCS	Ulcerative Colitis Clinical Score
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell(s)

Rationale for SAP amendment 2

The protocol was changed to include up to 400 additional patients with either ulcerative colitis or Crohn's disease who had not been previously treated with vedolizumab ("de novo patients"). The additional patients will increase the number of patients with exposure to vedolizumab and supplement the safety database to detect adverse events resulting from long-term vedolizumab administration that may not be detected in the year-long induction and maintenance studies. The addition of 400 patients allows for the detection of adverse events that occur at a prevalence of 0.1% to be detected with more than 85% likelihood, and events that occur at a prevalence of 1% to be detected with 99.99% likelihood. Importantly, the inclusion and exclusion criteria for the de novo patients are nearly identical to the criteria for patients who enrolled in Studies C13006, C13007, and C13011; study treatment and assessments are the same for these de novo patients as for rollover patients (those patients who enrolled in C13008 following participation in C13004, C13006, C13007, or C13011). The additional patients are enrolled at a subset of existing sites in select countries, including the United States (US).
In addition, with this protocol amendment, both rollover and de novo patients participating in C13008 will have access to vedolizumab until March 2016, or until vedolizumab is available in the country in which the patient resides , or until patient withdrawal, whichever comes first (unless the study is terminated early by the sponsor, as described in Section 11.12 of study protocol).

Another change to the protocol includes removal of JC virus DNA testing. When the vedolizumab pivotal studies were planned in 2008, it was unclear if JC virus DNA testing in the blood might be predictive of progressive multifocal leukoencephalopathy (PML) risk. More recently, controlled studies of natalizumab (which has a proven risk of PML) have conclusively demonstrated that detection of JC virus DNA in the blood is of no clinical utility in minimizing risk of PML. Therefore, monitoring for JC virus DNA in the blood has been discontinued.

Other changes to the protocol allow for the use of conventional, non-biological concomitant medications for IBD to be more consistent with standard clinical practice. Thus, patients are now allowed to start azathioprine, 6-mercaptopurine, methotrexate (methotrexate for CD only), or corticosteroids during the course of the study, even if they were not on these

medications when enrolled in the study. In addition, oral corticosteroid regimens have been modified to be more consistent with individual patient needs, and the corticosteroid tapering requirement has been changed to a recommendation.

The definition of treatment failure that mandates withdrawal from the study has been modified to "long-term treatment failure" to more accurately reflect true treatment failure that occurs in clinical practice. Given the fluctuating natural history of inflammatory bowel disease (IBD), patients may be treated for short-term disease worsening with conventional therapies for IBD, as allowed per protocol, without being required to withdraw from the study. Accordingly, one of the criteria for the protocol-defined treatment failure, "disease worsening," that was based on disease activity indices (Harvey-Bradshaw Index and partial Mayo score), has been removed from the definition of long-term treatment failure. Importantly, patients are still required to be withdrawn if they require rescue medication or major surgery for the treatment of IBD.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) presents a detailed plan for the analyses of the long-term safety and efficacy study C13008. The analysis is designed to evaluate the safety profile of long-term vedolizumab treatment.

The objectives of this analysis are stated in Section 1.2, and a discussion of the analyses to be performed is provided in Section 6.8 through Section 6.11.

Reference materials for this SAP include Clinical Study Protocol C13008 (Amendment 10 of the protocol, dated 15 February 2012) and the accompanying data collection documents (Annotated Case Report Form [CRF], final version, dated 07 May 2012).

1.1 Study Design

This is an open-label, phase 3 study to support the long-term safety and efficacy of vedolizumab for the treatment of patients with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD). All enrolled patients receive 300 mg vedolizumab administered every 4 weeks.

Most patients enrolling in this study have participated in a previous vedolizumab study (rollover patient).

- Patients with UC or CD who participated in the phase 2, open-label, long-term safety study (Study C13004), which includes up to 78 weeks of open-label treatment with vedolizumab.
- Patients who withdrew early from a phase 3 induction and maintenance study (Study C13006 [patients with UC] or Study C13007 [patients with CD]), which includes up to 50 weeks of blinded study treatment (vedolizumab or placebo). These patients must have withdrawn due to sustained non-response, disease worsening, or the need for rescue medications
- Patients who completed Study C13006 or Study C13007
- Patients who completed (through Week 10) Study C13011
- ~~Waiver patient(s)~~

For rollover patients, the first dose of vedolizumab in this study (Week 0) should occur no more than 9 weeks after the last dose of study drug in the previous study; the preferable period is within 3 to 5 weeks after the last dose in the previous study. Results of assessments from the last visit in the previous vedolizumab study are used to determine their eligibility to participate in this study. Baseline data are also obtained from the previous study, including medical history, disease history, demographics, tobacco use, and prior therapies.

In addition, up to 400 patients without previous treatment with vedolizumab are enrolled directly into this study (de novo patients). Patients with UC or CD must meet the inclusion/exclusion criteria for de novo patients (Section 5 of study protocol). Baseline data for these patients is obtained during the Screening period.

Following enrollment, all patients are administered 300 mg vedolizomab every 4 weeks for the duration of the study, followed by a 16-week post-treatment observation and safety assessment period. The total duration of MLN0002 treatment varies by patient based on continued benefit until March 2016, or until vedolizumab is available in the country in which the patient resides , or until patient withdrawal, whichever is sooner (unless the study is terminated early by the sponsor, as described in Section 11.12 of study protocol).

Patients may receive allowed concomitant medications for the treatment of IBD as detailed in Section 6.2.1 of study protocol, as determined by the principal investigator, at any time point during the study. Medications may be discontinued during the study, but if discontinuation is planned, it should be done prior to the first dose of vedolizumab.

It is strongly recommended that patients receiving oral corticosteroids begin an oral corticosteroid tapering regimen once they achieve clinical response or if, in the opinion of the investigator, they demonstrate sufficient improvement in clinical signs and symptoms.

Patients are withdrawn from the study for long-term treatment failure as described in the study definitions, or if they are not benefiting from therapy (see Section 6.2.3, Section 6.4.10, and Section 7.4 of study protocol).

All patients return 16 weeks after their last dose of MLN0002 for the Final Safety visit.

Safety assessments and efficacy assessments using the partial Mayo Score (for patients with UC) or the HBI score (for patients with CD) will be made throughout the treatment period.

Detailed visit-by-visit study procedures and assessments are provided in the Schedule of Events and Section 7 of study protocol.

This trial is conducted in compliance with the protocol, good clinical practice (GCP), and the applicable regulatory requirements (including International Conference on Harmonisation [ICH] guidelines).

1.2 Study Objectives

1.2.1 Primary Objective

- To determine the safety profile of long-term vedolizumab treatment

1.2.2 Resource Utilization and Patient Reported Outcome Objectives

- To determine the effect of long-term vedolizumab treatment on time to major inflammatory bowel disease (IBD)-related events (hospitalizations, surgeries, and procedures)
- To examine the effect of long-term vedolizumab treatment on health-related quality of life (QOL) measurements

1.2.3 Exploratory Objective

- To obtain data regarding the effect of long-term vedolizumab treatment on maintaining clinical response and remission based on partial Mayo score (for patients with UC) and Harvey-Bradshaw Index (HBI) (for patients with CD)

2. POPULATIONS FOR ANALYSIS

There will be 2 analysis populations: the safety population and the efficacy population.

2.1 Safety Population

The safety population for this study is defined as all patients who receive any amount of

vedolizumab in this study. Waiver patient(s) are excluded. The study safety population is used for all safety analyses.

Exposure for patients who first participated in Study C13004, C13006, C13007, or C13011 and who are now participating in the C13008 study, is evaluated from the first dose of vedolizumab in Studies C13004, C13006, C13007, and C13011.

For de novo patients, exposure is calculated from the first dose of vedolizumab in Study C13008.

Adverse events (AEs) are also evaluated from the first dose of vedolizumab in Studies C13004, C13006, C13007, and C13011 for the patients who received vedolizumab in Study C13004, C13006, C13007, or C13011. AEs are counted only during the time of vedolizumab administration, as follows:

- For patients who received placebo in Studies C13006, C13007, and C13011, AEs are counted from first dose of vedolizumab in the C13008 study.
- For patients who received vedolizumab in the induction phase and placebo in the maintenance phase, AEs are counted if the AE occurred between the first dose of vedolizumab and the last dose of vedolizumab in the induction phase.
- For patients who were in the placebo group in Study C13002, AEs are counted from the first dose of vedolizumab in the C13004 study.
- For patients who were in the vedolizumab group in Study C13002, AEs are counted from the first dose of vedolizumab in the C13002 study.
- For de novo patients, AEs are counted from the first dose of vedolizumab in the C13008 study.

Concomitant medications for patients who participated in Study C13004 and continue participating in Study C13008 are evaluated only for the C13008 experience, while the concomitant medications for patients who were in Studies C13006, C13007, and C13011 are evaluated following the administration of the first dose of vedolizumab in Studies C13006, C13007 and C13011.

Concomitant medications for de novo patients are evaluated from first dose onwards of vedolizumab in C13008 Study.

Other safety data, such as laboratory parameters, vital signs, and electrocardiograms (ECGs), are evaluated only for the C13008 experience.

The safety data from patients who participate in Study C13008 as waiver patient(s) will be included in the listings but will not be represented in the summary tables and figures.

2.2 Efficacy Population

The efficacy population consists of all enrolled patients. However, to be included in an analysis at any specific time point, the patient must have had a post-baseline measurement for the time point. Additionally, to be included in a change from baseline analysis, the patient must have had a baseline measurement. Waiver patient(s) who receive any amount of vedolizumab in this study are excluded from the efficacy population.

The efficacy data for patients who were in Study C13006 or C13007 and continue participating in C13008 is analyzed from the first efficacy assessment in C13006 or C13007 for the maintenance intent-to-treat (ITT) population and non-ITT population. The maintenance ITT population has 3 treatment groups : placebo, vedolizumab every 4 weeks (Q4 wks) dosing, and vedolizumab every 8 weeks (Q8 wks) dosing. The non-ITT population has 2 treatment groups: placebo and vedolizumab every 4 weeks (Q4 wks).

The efficacy data for patients who were in Study C13011 and continue participating in Study C13008 is analyzed from the first efficacy assessment in C13011 by vedolizumab and placebo treatment groups.

The efficacy data for de novo patients is analyzed for the C13008 experience.

All efficacy analyses is performed for patients who completed the previous Study C13006 or C13007 (52 weeks completers) or C13011 (10 weeks completers) and those who terminated early (early termination) from C13006 and C13007.

The efficacy data for patients who participated in Study C13004 and continue participating in C13008 is not analyzed.

The efficacy data from waiver patient(s) who participate in C13008 is included in the listings but is not included in the summary tables and figures.

The efficacy population is also used for all exploratory efficacy, resource utilization and patient reported outcome analyses.

3. HYPOTHESES AND DECISION RULES

The analyses are primarily descriptive in nature. Point estimations along with 95% confidence intervals are presented for important safety and efficacy parameters. No formal statistical hypothesis tests are performed.

4. INTERIM ANALYSIS

4.1 Interim Analysis

Two interim analyses will be conducted for safety at the time of BLA/MAA filing. Additional interim analyses on long-term safety data will be conducted for the Day 120 safety update(s).

4.2 Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) reviews safety data from this study including, but not limited to, incidence of AEs and AEs of special interest (eg, infusion-related reactions, infections) on a regular basis and makes appropriate recommendations to Millennium. A statistical reporting organization has been designated by Millennium to provide the DSMB with essential safety data during the study. The DSMB does not review the efficacy data. The DSMB responsibilities, authorities, and procedures are documented in a DSMB charter.

5. STUDY DEFINITIONS AND CONVENTIONS

5.1 Study Definitions

Study terms and definitions are provided below.

Pertaining to Patients with UC

Term	Definition
Clinical Remission	A partial Mayo score of ≤ 2 with no individual subscore > 1.
Clinical Response	A decrease in the partial Mayo Score of at least 2 points and ≥ 25% from baseline, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point from baseline or absolute rectal bleeding subscore of ≤ 1 point
Rescue Medication(s)	Any new medication to treat a new or unresolved luminal manifestation of ulcerative colitis (UC), with the following exceptions: □ oral and topical (rectal) 5-aminosalicylate (ASA) treatment □ oral corticosteroids per the guidelines outlined in Section 6.2.3 □ topical (rectal) corticosteroid enemas/suppositories □ azathioprine or 6-mercaptopurine; stable doses are recommended □ antibiotics □ antidiarrheals for control of chronic diarrhea • □ probiotics (eg, Culturelle, *Saccharomyces boulardii*)
Long-term Treatment Failure	Need for rescue medications, or major surgical intervention for treatment of UC, or a study drug-related adverse event leading to discontinuation from the study

Pertaining to Patients with CD

Term	Definition
Clinical Remission	A HBI score ≤ 4 points
Clinical Response	A ≥ 3-point decrease in HBI score from baseline
Rescue Medication(s)	Any new medication to treat a new or unresolved luminal manifestation of Crohn's disease (CD), with the following exceptions: • oral and topical (rectal) 5-ASA treatment

Term	Definition
	• oral corticosteroids per the guidelines outlined in Section 6.2.3 • topical (rectal) corticosteroid enemas/suppositories • azathioprine, 6-mercaptopurine, or methotrexate; stable doses are recommended • antibiotics • antidiarrheals for control of chronic diarrhea • probiotics (eg, Culturelle, *S. boulardii*)
Long-term Treatment Failure	Need for rescue medications, or major surgical intervention for treatment of CD, or a study drug-related adverse event leading to discontinuation from the study

5.2 Definition of Baseline Values

For partial Mayo score, HBI, and QOL variables, the baseline value is defined as the last assessments before the first dose of study drug administration from each previous study in Studies C13006, C13007, and C13011. For medical history, UC/CD disease history, tobacco use, and prior therapies, the baseline value is also obtained from the previous studies. For demographics, the baseline value is defined as the last assessment before the first induction dose in Study C13006, C13007, or C13011 (see Section 6.6). For the analyses of UC or CD, overall phase 3 clinical response, changes in partial Mayo score, and changes in HBI are based on the baseline calculated in Study C13006, C13007, or C13011.

For safety analyses, such as laboratory values, vital sign measurements, and ECGs, baseline is defined as the value collected at the last visit before the first dose of vedolizumab in Study C13008. For human anti-human antibody (HAHA) and C-reactive protein (CRP) data, baseline values are also obtained from the previous studies.

For de novo patients, the baseline value is defined as the last assessment before the first dose of vedolizumab in Study C13008.

5.2.1 Change and Percent Change From Baseline

Change from baseline to any treatment study Week t is defined as follows:

$C_t = M_t - M_{Baseline}$

where:

- C_t is the change from baseline at Week t
- M_t is the measurement at Week t
- $M_{Baseline}$ is the measurement at baseline

Percent change from baseline to any maintenance treatment study Week t is defined as follows:

$P_t = 100 \times (M_t - M_{Baseline}) / M_{Baseline}$.

The "Week t" to which the measurement belongs is determined using the conventions described in Section 5.3.

5.3 Visit Assignments

5.3.1 Study Start and End Dates

Enrollment is defined as the time at which the patient is entered into the Interactive Voice Response System (IVRS) for this study. Long-term safety study (C13008) treatment begins on the date of the first dose of study drug as recorded on the CRF.

Following enrollment, all patients are administered 300 mg vedolizumab every 4 weeks for the duration of the study , followed by a 16-week, post-treatment observation and safety assessment period. The total duration of vedolizumab treatment varies by patient based on continued benefit until March 2016, or until vedolizumab is available in the country in which the patient resides, or until patient withdrawal, whichever is sooner (unless the study is terminated early by the sponsor). The end of long-term treatment for patients who complete the study or who terminate early is defined as the date of the last known dose of vedolizumab during the C13008 study plus 16 weeks.

5.3.2 Visit Assignments for Efficacy Variables

Week assignment: Patients may not adhere strictly to the visit timing in the protocol. Therefore the designation of visits during the long-term safety is based on the day of evaluation relative to the start of the study rather than the nominal visit recorded in the CRF. Accordingly, the study is divided into continuous, mutually exclusive, analysis windows (Table 5-1), for the following efficacy measurements.

For efficacy parameters (partial Mayo score and HBI), if a patient has more than 1 score within a window, the assessment closest to the target day is used. In case of ties between observations located on different sides of the target day, the later assessment is used. If more than 1 score is available on the same day, the mean of the values is used.

Table 5-1 Day Windows: Partial Mayo Score and HBI Score for the Patients Who Were in Studies C13006 and C13007, and C13008 de novo patients

Visit in C13006/7	Target Day	Day Range
Week 2	15	2 - 21
Week 4	29	22 - 35
Week 6	43	36 - 56
Week 10	71	57 – 84
Week 14	99	85 – 112
Week 18	127	113 – 140
Week 22	155	141 – 168
Week 26	183	169 – 196
Week 30	211	197 – 224
Week 34	239	225 – 252
Week 38	267	253 – 280
Week 42	295	281 – 308
Week 46	323	309 – 336
Week 50	351	337 - 357
Week 52	365	358 - 392
Visit in C13008	**Target Day**	**Day Range**
Screening*		
Week 0*	1	-14
Week 4	29	15-42
Week 8	57	43-70
Week 12	85	71 – 112
Week 20	141	113 – 168
Week 28	197	169 – 224

Table 5-1 Day Windows: Partial Mayo Score and HBI Score for the Patients Who Were in Studies C13006 and C13007, and C13008 de novo patients

Week 36	253	225 – 280
Week 44	309	281 – 336
Week 52	365	337 – 392
Week 60	421	393 – 448
Week 68	477	449 – 504
Week 76	533	505 – 560
Week 84	589	561 – 616
Week 92	645	617 – 672
Week 100	701	673 - 728
Week 108	757	729-784
Week 116	813	785-840
Week 124	869	841 – 896
Week 132	925	897 – 952
Week 140	981	953 – 1008
Week 148	1037	1009 – 1064
Week 156	1093	1065 – 1120
Week 164	1149	1121 – 1176
Week 172	1205	1177 – 1232
Week 180	1261	1233 – 1288
Week 188	1317	1289 – 1344
Week 196	1373	1345 – 1400
Week 204	1429	1401-1456
Week 212	1485	1457-1512
Week 220	1541	1513-1568
Week 228	1597	1569-1624
Week 236	1653	1625-1680
Week 244	1709	1681-1722
Week 248	1737	1723-1764
Week 256	1793	1765-1820
Week 264	1849	1821-1876
Week 272	1905	1877-1932
Week 280	1961	1933-1988
Week 288	2017	1989-2044
Week 296	2073	2045-2086
Week 300	2101	2087-2128
Week 308	2157	2129-2184

Table 5-1 Day Windows: Partial Mayo Score and HBI Score for the Patients Who Were in Studies C13006 and C13007, and C13008 de novo patients

Week 316	2213	2185-2240
Week 324	2269	2241-2296
Week 332	2325	2297-2352
Week 340	2381	2353-2408
Week 348	2437	2409-2450
Week 352	2465	2451-2492

- For de novo patients, screening and week 0 are from nominal visit.

Table 5-2 Day Windows: HBI Score for the Patients Who Were in Study C13011

Visit in C13011	Target Day	Day Range
Week 2	15	2 - 28
Week 6	43	29-56
Week 10	71	57-84
Visit in C13008	**Target Day**	**Day Range**
Screening*		
Week 0*	1	-14
Week 4	29	15-42
Week 8	57	43-70
Week 12	85	71 – 112
Week 20	141	113 – 168
Week 28	197	169 – 224
Week 36	253	225 – 280
Week 44	309	281 – 336
Week 52	365	337 – 392
Week 60	421	393 – 448
Week 68	477	449 – 504
Week 76	533	505 – 560
Week 84	589	561 – 616
Week 92	645	617 – 672
Week 100	701	673 - 728
Week 108	757	729-784
Week 116	813	785-840
Week 124	869	841 – 896
Week 132	925	897 – 952
Week 140	981	953 – 1008
Week 148	1037	1009 – 1064

Table 5-2 Day Windows: HBI Score for the Patients Who Were in Study C13011

Week 156	1093	1065 – 1120
Week 164	1149	1121 – 1176
Week 172	1205	1177 – 1232
Week 180	1261	1233 – 1288
Week 188	1317	1289 – 1344
Week 196	1373	1345 – 1400
Week 204	1429	1401-1456
Week 212	1485	1457-1512
Week 220	1541	1513-1568
Week 228	1597	1569-1624
Week 236	1653	1625-1680
Week 244	1709	1681-1722
Week 248	1737	1723-1764
Week 256	1793	1765-1820
Week 264	1849	1821-1876
Week 272	1905	1877-1932
Week 280	1961	1933-1988
Week 288	2017	1989-2044
Week 296	2073	2045-2086
Week 300	2101	2087-2128
Week 308	2157	2129-2184
Week 316	2213	2185-2240
Week 324	2269	2241-2296
Week 332	2325	2297-2352
Week 340	2381	2353-2408
Week 348	2437	2409-2450
Week 352	2465	2451-2492

* For de novo patients, screening and week 0 are from nominal visit.

5.3.3Visit Assignments for Safety Variables

Table 5-3 Day Windows: JCV, Clinical Chemistry, and Hematology*

Visit in C13008	Target Day	Day Range
Screening**		
Week 4	29	2 – 56
Week 12	85	57 – 112

Table 5-3 Day Windows: JCV, Clinical Chemistry, and Hematology*

Visit in C13008	Target Day	Day Range
Week 20	141	113 – 168
Week 28	197	169 – 224
Week 36[a]	253	225 – 280
Week 44	309	281 – 336
Week 52[b]	365	337 – 392
Week 60	421	393 – 448
Week 68[a]	477	449 – 504
Week 76	533	505 – 560
Week 84	589	561 – 616
Week 92	645	617 – 672
Week 100[a]	701	673 – 728 (673 -- 756)[c]
Week 108	757	729-784
Week 116	813	785-840 (757-868)
Week 124	869	841 – 896
Week 132	925	897 – 952 (869 – 980)
Week 140	981	953 – 1008
Week 148	1037	1009 – 1064 (981- 1092)
Week 156	1093	1065 – 1120
Week 164	1149	1121 – 1176 (1093 -1204)
Week 172	1205	1177 – 1232
Week 180	1261	1233 – 1288 (1205 -1316)
Week 188	1317	1289 – 1344
Week 196	1373	1345 – 1421 (1317 -1428)
Week 212	1485	1429-1540
Week 228	1597	1541-1666
Week 248	1737	1667-1792
Week 264	1849	1793-1904
Week 280	1961	1905-2030
Week 300	2101	2031-2156
Week 316	2213	2157-2268
Week 332	2325	2269-2394
Week 352	2465	2395-2535

* JCV assessment, clinical chemistry and hematology are not conducted at Day 0. For baseline, the last measurement from the previous study (eg, C13004, C13006, C13007, or C13011) is used.

** For de novo patients, screening and week 0 are from nominal visit.

a Schedule for CRP follows Weeks 36, 68, 100, 132, 164, and 196 visits window above.

b Schedule for coagulation follows Week 52, 104, and 152 visit window above.

c Windows in the brackets are for clinical chemistry and hematology in Years 3 and 4 only. . JCV testing

Table 5-3 Day Windows: JCV, Clinical Chemistry, and Hematology*

Visit in C13008	Target Day	Day Range

was discontinued per protocol amendment 8. No JCV testing beyond Week 196.

Duplicate laboratory assessments: If the same parameter is reported more than once on the same date, the mean of that parameter is used in the analyses. If a patient has more than 1 measure within a visit but on different dates, the assessment closest to the target day is used. In case of ties between observations located on different sides of the target day, the later assessment is used. In case of ties located on the same side of the target day (ie, more than 1 value for the same day), the mean of the values is used. For HAHA and CRP, if a patient has more than 1 measurement within the same study day, the highest value is used.

For JCV, if a patient has more than 1 measurement within an analysis window, the positive assessment value is chosen over a negative JCV value regardless of the target date. If more than 2 negative JCVs are within the same window, the 1 closest to the target date is used. If more than 2 positive JCVs are within the same window, the 1 with the higher titer value is chosen over the 1 with lower titer value. For duplicate vital sign parameters, the same rule as above is followed.

Table 5-4 Study Visit Windows: Vital Signs

Visit in C13008	Target Day	Day Range
Screening*		
Week 0*		
Week 4	29	2 – 42
Week 8	57	43 – 70
Week 12	85	71 – 98
Week 16	113	99 – 126
Week 20	141	127 – 154
Week 24	169	155 – 182
Week 28	197	183 – 210
Week 32	225	211 – 238
Week 36	253	239 – 266
Week 40	281	267 – 294
Week 44	309	295 – 322
Week 48	337	323 – 350
Week 52	365	351 – 378
Week 56	393	379 – 406

Table 5-4 Study Visit Windows: Vital Signs

Visit in C13008	Target Day	Day Range
Week 60	421	407 – 434
Week 64	449	435 – 462
Week 68	477	463 – 490
Week 72	505	491 – 518
Week 76	533	519 – 546
Week 80	561	547 – 574
Week 84	589	575 – 602
Week 88	617	603 – 630
Week 92	645	631 – 658
Week 96	673	659 – 686
Week 100	701	687 – 714
Week 104	729	715 – 742
Week 108	757	743 – 770
Week 112	785	771 – 798
Week 116	813	799 – 826
Week 120	841	827 – 854
Week 124	869	855 – 882
Week 128	897	883 – 910
Week 132	925	911 – 938
Week 136	953	939 – 966
Week 140	981	967 – 994
Week 144	1009	995 – 1022
Week 148	1037	1023 – 1050
Week 152	1065	1051 – 1078
Week 156	1093	1079 – 1106
Week 160	1121	1107 – 1134
Week 164	1149	1135 – 1162
Week 168	1177	1163 – 1190
Week 172	1205	1191 – 1218
Week 176	1233	1219 – 1246
Week 180	1261	1247 – 1274
Week 184	1289	1275 – 1302
Week 188	1317	1303 – 1330
Week 192	1345	1331 – 1358
Week 196	1373	1359 – 1386
Week 200	1401	1387-1414
Week 204	1429	1415-1442

Table 5-4 Study Visit Windows: Vital Signs

Visit in C13008	Target Day	Day Range
Week 208	1457	1443-1470
Week 212	1485	1471-1498
Week 216	1513	1499-1526
Week 220	1541	1527-1554
Week 224	1569	1555-1582
Week 228	1597	1583-1610
Week 232	1625	1611-1638
Week 236	1653	1639-1666
Week 240	1681	1667-1694
Week 244	1709	1695-1722
Week 248	1737	1723-1750
Week 252	1765	1751-1778
Week 256	1793	1779-1806
Week 260	1821	1807-1834
Week 264	1849	1835-1862
Week 268	1877	1863-1890
Week 272	1905	1891-1918
Week 276	1933	1919--1946
Week 280	1961	1947-1974
Week 284	1989	1975-2002
Week 288	2017	2003-2030
Week 292	2045	2031-2058
Week 296	2073	2059-2086
Week 300	2101	2087-2114
Week 304	2129	2115-2142
Week 308	2157	2143-2170
Week 312	2185	2171-2198
Week 316	2213	2199-2226
Week 320	2241	2227-2254
Week 324	2269	2255-2282
Week 328	2297	2283-2310
Week 332	2325	2311-2338
Week 336	2353	2339-2366
Week 340	2381	2367-2394
Week 344	2409	2395-2422
Week 348	2437	2423-2450
Week 352	2465	2451-2478

*For de novo patients, screening and week 0 are from nominal visit.

For parameters that are not listed in the above tables, data collected from scheduled visits are analyzed by the nominal visit week as labeled in the CRF. Data collected from unscheduled visits are presented in the listings, but not summarized in the pre-planned analysis. For example, IBDQ, SF-36, EQ-5D, and HAHA data are analyzed by the nominal visit week as labeled in the CRF.

Duplicates in Quality of Life Parameters: For handling partial and complete questionnaire data, when multiple records of the same type are present for a visit, the following conventions are used:

- If 1 complete score (all components and total [where applicable]) and 1 partial score (at least 1 missing component) are available for the same visit, the complete score is used—regardless of proximity to target date.
- If 2 partial scores are available, for overlapping components, the score from the date closest to the target date is given precedence for the given component. Components can be mixed from the 2 dates (if available components differ) and a new total calculated.
- If more than 1 complete score is available for the same visit, the data from the date closest to the target date is used.
- If partial scores are on separate dates but are the same proximity to the target date, the latest partial date is used.

5.3.4 Conventions for Missing Adverse Event Dates

Every effort is made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or SAEs, a missing or incomplete onset date is imputed according to the following conventions:

1. If an onset date is missing, the derived onset date is calculated as the first non-missing valid date from the following list (in order of precedence):

- First vedolizumab dose date
- Consent date (for SAEs only)

2. If an onset date is incomplete, the derived onset date is calculated by the following:

   - Missing day, but month and year present: the day is imputed as the 15th of the month. If the month and year are equal to the month and year of the first vedolizumab dose and the first vedolizumab dose occurs after the imputed date, the derived onset date is set equal to the first vedolizumab date. If the AE end date occurs before the imputed date, the derived onset date is set equal to the AE end date.
   - Missing day and month, but year present: the day and month is imputed as the 30th June of the year. If the year is equal to the year of the first vedolizumab dose and the first vedolizumab dose occurs after the imputed date, the derived onset date is set equal to the first vedolizumab date. If the AE end date occurs before the imputed date, the derived onset date is set equal to the AE end date.
   - If the imputed AE onset date occurs after the database lock date, the imputed AE onset date is imputed as the database lock date.

For AEs or SAEs, a missing or incomplete end date is imputed according to the following conventions:

1. If an end date is missing, the derived end date is imputed as the last assessment date, assuming that the last assessment occurs after the AE start. If the last assessment occurs before the AE start date, the derived end date is imputed as the AE start date.

2. If an end date is incomplete, the derived end date is calculated by the following:

   - Missing day, but month and year present: the day is imputed as the last date (for example February 2009 is imputed as 28 February 2009) of the month.
   - Missing day and month, but year present: the day and month is imputed as the 31st December of the year.
   - If the imputed AE end date occurs after the database lock date, the imputed AE end date is imputed as the database lock date.

Missing dates for hospitalizations for UC or CD, colectomies (UC) or bowel surgeries (CD), and UC or CD procedures follow the same rules as previously defined.

5.3.5 Conventions for Missing Concomitant Medication Dates

Start and stop dates for all concomitant medications are collected on the CRF. However, in the case of missing or partial information in these dates, the following rules are used:

If the start date is missing or partial:

- If the day is missing, the start day is the first day of the month.
- If the month is missing, the start month is the month corresponding to 90 days before the first study medication date.
- If the year is missing, the start year is the year of the entry visit (or consent date, for those missing entry visit).
- If the entire date is missing, the start date is the date of first vedolizumab administration.

If the stop date is missing, partial, or "continuing:"

- If the day is missing, the stop day is the last day of the month reported.
- If the month is missing, the stop month is the month during which the last assessment occurred.
- If the year or the entire date is missing or if the medication is "continuing", the stop year is the year in which the last assessment occurred.

5.3.6 Conventions for Missing Previous Medication Dates

No dates are imputed for previous medications.

5.4 Calculation of Body Mass Index

Millennium calculates BMI as the ratio of patient's weight (in kilograms) to the square of the patient's height (in meters): BMI = kg/m^2.

6. STATISTICAL METHODOLOGY

6.1 Determination of Sample Size for the Long-term Safety Study

This is a phase 3 study to determine the long-term safety of vedolizumab (MLN0002) in patients with UC and CD. Most patients enrolled in this study have participated in a previous qualifying MLN0002 study as detailed in Section 4.1 (rollover patients). Up to 400 additional patients who have not been previously treated with vedolizumab may be enrolled (de novo patients) to supplement the safety database. The current estimate is that approximately 2200 patients in total will enter this study.

6.2 Randomization and Stratification

No randomization or stratification is planned for this study.

6.3 Unblinding

This is an open-label study; there is no blinding.

6.4 Methods for Handling Missing Data

All available safety and efficacy data are included in data listings and tabulations. No imputation of values for missing data are performed, except as described within this statistical analysis plan.

All patients who prematurely discontinue for any reason are considered censored for time to event type of analyses and endpoints.

6.5 Patient Disposition

Patient disposition is summarized by study:

- Patients who were in C13004 study,
- Patients who were in C13006 study,
- Patients who were in C13007 study
- Patients who were in C13011 study

- De novo patients in C13008 study

In addition to the above 5 groups, safety data is also summarized by the following subgroups:

- By indication: UC and CD
- By prior TNF-α failures (Yes/No)

Data for waiver patients are not presented in the summary tables, but are displayed in the listings.

The disposition table displays the number of patients in:

- Safety Population
- Efficacy Population
- Prior TNF failure population
- Early termination from prior study
- Completed prior study
- Ongoing Patients
- Completed Long-term Safety Study
- Not Completing Long-term Safety Study, Primary Reasons

Patients who discontinued from the C13008 study are listed. This listing uses the safety population.

6.6 Demographics and Baseline Disease Characteristics

6.6.1 Demographics

For demographic characteristics, the baseline value is defined as the last assessment before the first induction dose of blinded study drug (C13006, C13007, or C13011) and the first dose of vedolizumab (C13004) or the assessment at screening for de novo patients.

Demographic baseline data, such as age, gender, race, and ethnicity (Hispanic/Latino and non-Hispanic/Latino), body weight, BMI, and geographic region (as defined in Appendix 3) are summarized overall and by the 3 categories as defined in Section 6.5, using the safety population. Patient baseline age and BMI are summarized as continuous variables.

For baseline disease characteristics, UC- or CD-related medical and disease history and QOL baseline variables, the values are defined as the last assessments before the first dose of study drug administration in previous Studies C13004, C13006, C13007, and C13011. For de novo patients, the values at screening are used.

Disease-specific baseline disease characteristics are summarized by UC and CD indication, and by the categories as defined in Section 6.5.

Table 6-1 Summaries of UC/CD-Related Baseline Characteristics

Characteristic	Summarized as	Categories
Duration of Crohn's Disease (CD only)	Continuous	
Duration of Ulcerative Colitis (UC only)	Continuous	
Categorical Duration of Ulcerative Colitis (UC only)	Categorical	< 1 year, ≥ 1- < 3 years, ≥3- < 7 years
Categorical Duration of Crohn's Disease (CD only)	Categorical	< 1 year, ≥ 1- < 3 years, ≥ 3-7 years, missing
Patients with prior TNF α use	Categorical	Yes/No
Patients with prior TNFα failure	Categorical	Yes/No
Patients with TNF α and immunomodulator failure	Categorical	Yes/No
Patients with corticosteroid or immunomodulator	Categorical	Yes/No
Patients with only concomitant corticosteroid	Categorical	Yes/No
Patients with only concomitant immunomodulator	Categorical	Yes/No
Patients with concomitant corticosteroid and Immunomodulator	Categorical	Yes/No
Patients with concomitant corticosteroid	Categorical	Yes/No
Patients with concomitant immunomodulator	Categorical	Yes/No
HBI (CD only)	Continuous	

Table 6-1 Summaries of UC/CD-Related Baseline Characteristics

Characteristic	Summarized as	Categories
CRP (CD only)	Continuous	
Fistulizing Disease (CD only)	Categorical	Yes/No
Smoking Status	Categorical	Current Smoker
		Nonsmoker
		Former Smoker
Partial Mayo Score (UC only)	Continuous	
Baseline of Extraintestinal Manifestations(UC only)	Categorical	Yes/No
Baseline of Extraintestinal Manifestations(CD only)	Categorical	Yes/No

For categorical characteristics, percent is calculated out of the total number of patients in the data set, overall and by subcohorts.

Duration of UC or CD is calculated as below:

(1 + C13008 first dose date – diagnosis date from C13004/006/007/011)/ 365.25.

For de novo patients, duration of UC or CD is calculated as (1 + C13008 first dose date – diagnosis date)/ 365.25.

Demographics are presented in listings for each patient in the safety population.

6.7 Treatments and Medications

6.7.1 Concomitant Medications and Procedures

Concomitant medication is defined as medication, any amount of which is taken between the first and last day-(inclusive) of vedolizumab administration. Concomitant procedures are similarly defined.

Concomitant medications are summarized for the safety population by drug class (ATC Pharmacological subgroup), generic drug name, and patient categories as defined in Section 6.5. Concomitant medication use is also presented in listings.

Concomitant procedures are not coded, but presented in listings for each patient in the safety population.

6.7.2 Study Drug Administration

Patients receive open-label vedolizumab by intravenous (IV) infusion.

6.7.2.1 Extent of Exposure

Extent of exposure is defined as the number of complete infusions a patient receives. A patient must receive at least 75% of an infusion for it to be considered complete.

Exposure to study drug is defined as the number of days the patient received study drug based on the first and last doses regardless of in which study the beginning or end of dosing occurred. Given Q8 week dosing schedule, exposure also includes an additional 56 days after the last dose:

Exposure = (date of last infusion – date of first infusion) + 56

The cumulative distribution of the number of months on study drug (categorized by ≥ 1 month, ≥ 6 months, ≥ 12 months, ≥ 18 months, ≥ 24 months, ≥ 30 months, and ≥ 36 months) is provided as well as the cumulative distribution of the infusions.

The exposure presentations are provided for overall (CD and UC combined) and by indication. The overall vedolizumab experience includes the exposure to vedolizumab in all the trials (double-blind: C13006, C13007, and C13011 and open-label: C13002-C13004 and C13008).

The following rules are set up as referenced by the Request for Information FDA Advisory Committee April 2011.

General Rules:

- Last Dose Date in Induction is defined as the latest dose date entered into Inform, before the maintenance randomization date.
- Last Dose Date on Study is defined as the latest dose date entered into Inform.
- Methods are heavily reliant on data being entered into InForm.

Exposure Calculation Rules for Incorporating Up to 16 Week PK/PD Effect

C13006/7 Patients

- Calculate exposure for C13006/7 and C13008 separately and sum.
- For C13006/7:
    - If on placebo in Induction in C13006/7, then C13006/7 EXPOSURE = 0
    - If on drug in Induction only (and not on drug in Maintenance):
        - Calculate C13006/7 End Exposure Date as min((Last Dose in Induction + 16 weeks), C13008 Start Date)
        - C13006/7 EXPOSURE = (C13006/7 End Exposure Date – First Dose in Induction + 1)
    - If on drug in Induction & Maintenance:
        - Calculate C13006/7 End Exposure Date as min (Last Dose in Maintenance + 16 weeks, C13008 Start Date)
        - C13006/7 EXPOSURE = (C13006/7 End Exposure Date – First Dose in Induction + 1)
- For C13008:
    - End exposure date = min((Last Dose Date on C13008 + 16 weeks), Data Cutoff Date)
    - C13008 EXPOSURE = (End Exposure Date-First Dose Date in C13008 + 1)
- TOTAL EXPOSURE = C13006/7 EXPOSURE + C13008 EXPOSURE

C13011 Patients

- Calculate exposure for C13011 and C13008 separately and sum.
- For C13011:

  - If placebo in C13011, then C13011 EXPOSURE = 0
  - Calculate C13011 End Exposure Date as min ((Last Dose in Induction in C13011 + 16 weeks), C13008 Start Date)
  - C13011 EXPOSURE = (C13011 End Exposure Date – First Dose in Induction + 1)

- For C13008:
  - End exposure date = min((Last Dose Date on C13008 + 16 weeks), Data Cutoff Date)
  - C13008 EXPOSURE = (End Exposure Date-First Dose Date in C13008 + 1)

- TOTAL EXPOSURE = C13011 EXPOSURE + C13008 EXPOSURE

C13002/4 Patients

For patients who have rolled over into C13008:

- For C13002/4:
  - Calculate C13002 End Exposure Date as min ((Last Dose in C13002 + 16 weeks), C13004 Start Date)
  - Calculate C13004 End Exposure Date as min ((Last Dose in C13004 + 16 weeks), C13008 Start Date)
  - If not in C13002 or on placebo in C13002, C13002/4 EXPOSURE = C13004 End Exposure Date - First Dose Date in C13004 + 1
  - If on drug in C13002, C13002/4 EXPOSURE = (C13004 End Exposure Date - First Dose Date in C13004 + 1) + (C13002 End Exposure Date – First Dose Date in C13002 + 1)

- For C13008:
  - Calculate C13008 End Exposure Date as min((Last Dose in C13008 + 16 weeks), C13008 Data Cutoff Date)

- C13008 EXPOSURE = (C13008 End Exposure Date-First Dose Date in C13008 + 1)

TOTAL EXPOSURE = C13002/4 EXPOSURE + C13008 EXPOSURE

Exposure is also calculated incorporating up to 8 weeks (56 days). The same rules as above are applied but by adding 8 weeks instead of 16 weeks in the calculations.

Exposure Calculation Rules Without Incorporating Up to 16 Week PK/PD Effect

In addition, exposure without incorporating up to 16 week PK/PD effect post last dose is calculated as below.

Use the exposure calculation rules above with the following modifications:

1. Do not add 16 weeks at any point in the calculations.
2. For patients C13006/7/11 on drug in induction only, calculate the end of exposure date as min (last dose date in induction + 4 weeks, C13008 start date).
3. For patients C13006/7 on drug in induction and maintenance, calculate the end of exposure date as min (last dose date in maintenance + 2 weeks, C13008 start date).

For de novo patients, the following rule is used to calculate exposure (in days):

- End exposure date = min((Last Dose Date on C13008 + 16 weeks), Data Cutoff Date)
- C13008 EXPOSURE = (End Exposure Date-First Dose Date in C13008 + 1)

Extent of exposure for the long-term safety treatment is listed by patient.

6.8 Safety Analyses

Summaries of safety data such as Lab, JCV, RAMP, vital, PML checklist responses, and ECG are provided for data collected on patients during Study C13008 up to the final safety visit. These analyses are performed using the safety population.

Summary of AEs, SAE, and infections are based on the safety population as described in Section 2.1. In addition to incidence rates, rates of certain AEs, such as infections, are expressed in terms of time adjusted incidence rates (eg, events/person-year) to accommodate variable patient follow-up time and recurrent AEs within the same patient.

No statistical tests are performed.

6.8.1 Safety Data Summary Grouping for Long-term Safety Study

AE incidence rates and other safety parameters are summarized for all C13002/4/6/7/8/11 patients, and by the patient groups defined in Section 6.5. In addition, incidence rates are summarized by CD and UC.

The comprehensive safety assessment as described in Section 8.7 of the C13008 Protocol Amendment 10 will be covered by the integrated safety summary that will have a separate analysis plan.

6.8.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) is used for coding AEs. To summarize the number of patients with AEs, patients reporting the same event more than once has that event counted only once within each system organ class (SOC), high-level term (HLT), and preferred term (PT).

Key guidelines for the selection of AE incident rates for counting are as follows:

1. Where a patient has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the patient is counted only once in the preferred terminology level in AE tables.

2. When a patient has the same AE, based on preferred terminology, reported multiple times in a single analysis phase, the following criteria, in order of precedence, are used to select the event to be included in summary tables.

    - Relationship to study medication

    - Intensity of event

    - Onset date and time (the earlier onset date and time are selected for the incident rates)

3. When reporting AE incident rates by intensity, the most intense event during the analysis phase is summarized, independent of relationship to study medication. For

these tables, the following criteria, in order of precedence, are used to select the event to be included in summary tables.

- Intensity of event
- Onset date and time (the earlier onset date and time are selected for the incident rates)

For any AE (serious or not), onset of the AE is determined using the Conventions outlined in Section 5.3.4.

In summaries by SOC, HLT, and PT, AEs are sorted by decreasing frequency of each PT, HLT, and SOC according to the incident rates. In summaries by PT, AEs are sorted by decreasing frequency within PT according to the incident rates.

6.8.2.1 Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as any new medical event/finding that occurs after the first vedolizumab administration in C13002/4/6/7/8/11 as recorded on the CRF.

6.8.2.2 Time Adjusted Incidence Rates

To provide a benchmark for evaluation of AEs reported in the long-term safety study, a cohort study was performed on data from an external administrative database (HealthCore Integrated Research Database, HIRD^{TM}), which includes a broad representation of patients on various therapies for IBD including biological agents. These analyses will provide estimates of the background rates of AEs of special interest.

For the analysis of the HIRD and Study C13008, the time adjusted incidence rate is defined as the number of patients experiencing an AE of interest divided by the person-time at risk. The amount of person-time will be truncated after a patient experiences an adverse event of special interest, although that patient will continue to contribute person-time for unrelated adverse events of special interest.

AE of special interest can be found in Appendix 8. The final list for AEs of special interest will depend on the results of Study C13008.

6.8.2.3 All Adverse Events

AE incidence rates are summarized by SOC, HLT, PT, and by the groups defined in Section 6.5.

All reported AEs during the long-term safety study are listed by the groups defined in Section 6.5.

6.8.2.4 Serious Adverse Events

Serious adverse event (SAE) incident rates are presented by SOC, HLT, PT, and by the groups defined in Section 6.5. In addition, related SAE incident rates are presented by SOC, HLT, PT, and by the groups defined in Section 6.5.

All SAEs are listed by the groups defined in Section 6.5.

6.8.2.5 Deaths

All on-study deaths recorded on the AE page (outcome), or death page (with a death date and cause of death) of the CRF are considered in the analyses. All deaths are summarized by PT for the total patient group. All deaths are listed.

6.8.2.6 Adverse Events Resulting in Discontinuation of Study Drug

AEs reported with an action taken of "discontinuation of study drug" are summarized by SOC, HLT, PT, and the groups defined in Section 6.5. Adverse events resulting in discontinuation of study are also summarized by SOC, HLT, PT, and CD/UC subgroups as defined in Section 6.5.

In addition, all AEs leading to discontinuation of study drug are listed.

6.8.2.7 Adverse Events of Special Interest

Based on the mechanism of action of vedolizumab, certain adverse events and safety laboratories are of special interest. AEs of special interest include unusual or opportunistic infections, serious infections, and neoplasms. AEs of special interest are summarized by MedDRA SOC, HLT, and PT according to the groups defined in Section 6.5. Separately,

some AEs of special interest are also summarized by SOC, HLT, PT, and CD/UC subgroups as defined in Section 6.5.

The categories of adverse events of special interest and other planned analyses are as follows:

Infections

Summary tables of all serious infections and infections leading to discontinuation of study drug are presented . As vedolizumab is a local immunomodulator of the gastrointestinal tract, mucosal and gastrointestinal infections are also summarized separately. TEAE infections are also listed. Incidence of infections are summarized by the groups defined in Section 6.5. Infection rates are summarized by SOC, HLT, PT, and CD/UC subgroups as defined in Section 6.5.

Infections are also presented by time adjusted incidence rate (eg, events/person years).

Comparative rates of infection in patients who have not received concomitant immunomodulators or concomitant corticosteroids (monotherapy) , patients who have received concomitant immunomodulators (eg, azathioprine, 6-mercaptopurine), and patients who have received concomitant corticosteroids (eg, prednisone, prednisolone), are reported.

Gastrointestinal Adverse Events

Subset analyses of all gastrointestinal AEs include all serious AEs and gastrointestinal AEs leading to discontinuations. Gastrointestinal AE incident rates are summarized by the patient groups defined in Section 6.5.

Infusion-Related Reactions/Immunogenicity

Infusion-related AEs are summarized by PT and the patient groups defined in Section 6.5. In addition, all AEs beginning on or 1 calendar day after the dates of study drug infusions are similarly analyzed. Comparative rates of infusion-related AEs are reported in HAHA-negative and HAHA- positive patients (see Section 6.8.6.3). Comparative rates of infusion-related AEs are also reported by CD/UC subgroups as defined in Section 6.5. Infusion-related AEs (investigator defined) are presented by preferred term.

Safety Related to Risk Management (RAMP Algorithm, JC Viremia, and Long-term Follow-up Data)

The protocol incorporates an active screening program to identify and manage any case of progressive multifocal leukencephalopathy (Protocol Section 10.5.3). This program is known as the Risk Assessment and Minimization for PML (or RAMP). In addition to the RAMP, plasma specimens were collected during the study and assayed for JC virus (JCV). However, JCV testing was discontinued per protocol amendment 8.

The results of the RAMP screening program are summarized for the patient groups defined in Section 6.5. Results of JCV testing are also summarized for the overall patient group. The RAMP algorithm findings are also listed.

Summary tables for long-term follow-up data are summarized.

Neoplasms (Benign, Malignant, and Unspecified)

All neoplasms are summarized overall, by patient groups, and by CD/UC subgroups as defined in Section 6.5.

Liver Function Tests

Descriptive statistics and shift tables for all liver function test results are reported, and all liver function abnormalities reported as AEs are summarized by the patient cohorts described in Section 6.5. In addition, the percentage of subjects who develop categorical increases (≤ 1, > 1 x ULN to ≤ 2 x ULN; > 2 x ULN to ≤ 3 X ULN, > 3 x ULN to ≤ 5 x ULN and > 5) in ALT, AST, or bilirubin are summarized. Individual narratives are written for patients with evidence of significant liver dysfunction.

Hematology

Descriptive statistics and shift tables for each subtype of white blood cell (ie, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) are summarized by the patient groups defined in Section 6.5.

6.8.2.8 Adverse Events in Special Groups

AEs by preferred term are presented separately based on the special groups listed below:

- Age (< 65, ≥ 65 years)
- Race (White, Black, Asian, and Other)
- Sex (Male, Female)
- Baseline disease activity (moderate [UC: Baseline Partial Mayo Score < 6, CD: CDAI < 330], severe [UC: Baseline Partial Mayo Score ≥ 6, CD: CDAI ≥ 330])
- Body Weight (< 70 kg, 70-90 kg, > 90 kg)

6.8.3 Laboratory Data

Unless otherwise specified, laboratory data obtained on and after Week 4 in the long-term safety study are included in the summary tables. Additionally, since laboratory tests will not be restricted to scheduled visits, Section 0 provides uniform visit windows to link each laboratory test to a scheduled visit. Assignment of patient treatment to a laboratory measurement is described in Section 0.

For the purposes of summarization in both the tables and listings, all laboratory values are converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value is used in the summary statistics, ignoring the non-numeric qualifier. All laboratory data are summarized by the patient groups defined in Section 6.5.

6.8.3.1 Marked Laboratory Abnormalities

Laboratory abnormalities are evaluated based on marked abnormality (MA) criteria. Appendix 2 (Laboratory Abnormality Criteria) lists the predefined criteria for MAs. If both the baseline and on-treatment values of a parameter are beyond the same MA limit for that parameter, then the on-treatment value is considered an MA only if it is more extreme (farther from the limit) than the baseline value. If the baseline value is beyond the low MA limit and the on-treatment value is beyond the high MA limit (or vice versa), then the on-treatment value is considered a MA.

Laboratory MAs occurring during the long-term safety study are summarized. The directions of changes (high or low) in MAs are indicated in the tables. Additionally, for

each patient with an MA for a parameter, all the patient's values of that parameter over the long-term safety study are listed.

6.8.3.2 Changes from Baseline Values for Selected Laboratory Parameters over Time

The following hematology parameters and their changes from baseline values are summarized over all scheduled times of assessment, presenting n, means, medians, standard deviations and 95% CIs.

- hematocrit (changes from baseline)
- hemoglobin (changes from baseline)
- platelet count (changes from baseline)
- red blood cell (RBC) count (changes from baseline)
- white blood cell (WBC) count (changes from baseline)
- absolute neutrophil count (ANC) (changes from baseline)
- absolute lymphocyte count (changes and percent changes from baseline)
- absolute monocyte counts (changes and percent changes from baseline)
- absolute eosinophil counts (changes and percent changes from baseline)
- absolute basophil counts (changes and percent changes from baseline)

The following serum chemistry parameters and their change from baseline values are summarized over all scheduled times of assessment, presenting n, means, medians, standard deviations, and 95% CIs:

- total and direct bilirubin (changes from baseline)
- alanine aminotransferase (ALT) (changes from baseline)
- alkaline phosphatase (changes from baseline)

- aspartate aminotransferase (AST) (changes from baseline)
- amylase (changes from baseline)
- bicarbonate (changes from baseline)
- blood urea nitrogen (BUN) (changes from baseline).
- creatinine, serum (S_{cr}) (changes from baseline)
- calcium (changes from baseline)
- glucose (changes from baseline)
- lipase (changes from baseline)
- magnesium (changes from baseline)
- phosphorus (changes from baseline)
- electrolytes - sodium, potassium, chloride, (changes from baseline)
- total protein and albumin (changes from baseline)
- coagulation (changes from baseline)

Baseline is defined as the value collected at the last visit prior to the first dose of vedolizumab administration in C13008 study. The baseline and the visit window defined in Section 0 is followed for this calculation. For patients who were in C13004, the last measurement from C13004 is used for the baseline. For de novo patients, the assessments at screening are used for the baseline.

6.8.4 ECG

Percent of subjects with abnormal ECGs are summarized by study visits. ECG abnormalities reported as AEs are summarized in the AE analysis as specified in Section 6.8.2.

6.8.5 Vital Signs

The values and changes from baseline for heart rate, temperature, respiratory rate, and systolic and diastolic blood pressure are summarized by the patient groups defined in Section 6.5 at each scheduled time of assessment using the safety population. Vital sign abnormalities reported as AEs are summarized in the AE analysis as specified in Section 6.8.2.

6.8.6 Immunogenicity Analysis

6.8.6.1 Data Set Analyzed

HAHA baseline data is taken from the last measurements of the previous study (eg, C13004, C13006, C13007, or C13011) since HAHA is not measure on Day 0 of Study C13008. For de novo patients, the HAHA at screening is used for the baseline. Vedolizumab serum concentrations and HAHA data are summarized by study visits and by the patient groups defined in Section 6.5 using the safety population. Listings of vedolizumab and HAHA are also included. Serum concentration below limit of quantification is set to zero. No imputation is performed.

6.8.6.2 HAHA Definitions

Negative HAHA

A sample that has been evaluated as negative in the HAHA screening assay is considered negative. Samples that are determined to be positive in the HAHA screening assay, but the result is not confirmed in the HAHA confirmatory assay is considered negative.

Positive HAHA

A sample that has been evaluated as positive in both the HAHA screening and confirmatory assays is considered positive.

Positive Neutralizing HAHA

A sample that has been evaluated as positive in the neutralizing HAHA assay is considered positive.

6.8.6.3 Patient Status

Baseline Positive

All patients who are HAHA positive from measurements from the previous study (eg, C13004, C13006, C13007, or C13011) are defined as baseline positive.

Patient HAHA status is further categorized and summarized as follows:

Negative

All patients who have no positive HAHA sample.

Positive

All patients who have at least 1 positive HAHA sample.

Persistent Positive

All patients who have 2 or more consecutive positive HAHA samples.

The maximum HAHA titer and percentage of subjects with each HAHA status are presented overall and by the patient groups defined in Section 6.5. Additional HAHA titer categories (eg, titer ≥ 5, ≥ 15, ≥ 45, ≥ 125, ≥ 625, and ≥ 3125) are summarized if deemed appropriate.

6.8.6.4 Effects of HAHA on Safety

Summary of overall AEs by HAHA status is presented. Summary of infusion-related AEs by HAHA status is also reported.

6.9 Exploratory Efficacy Analyses

This section describes the analyses conducted on the exploratory efficacy, resource utilization, and patient-reported outcome endpoints.

6.9.1 General Methods

The primary statistical focus for the exploratory efficacy analyses is on descriptive summary of efficacy endpoints rather than on formal analysis of the clinical data. Descriptive statistics, including 95% CIs, are provided for all clinical efficacy variables of interest.

The exploratory efficacy summaries are carried out using the baseline defined in Section 5.2. The exploratory efficacy analyses use the C13008 efficacy population.

6.9.2 Exploratory Efficacy Endpoints

The following exploratory efficacy variables are summarized by study visits:

- HBI score (CD only)
- Proportions of HBI score ≤ 4, 4 < HBI score ≤ 7 and HBI score > 7
- Partial Mayo score (UC only)
- Proportions of Partial Mayo score ≤ 2, 3 ≤ partial Mayo score ≤ 5 and partial Mayo score ≥ 6
- CRP levels (CD only)

6.9.3 Exploratory Efficacy Analysis

The descriptive statistics for observed values and change from baseline in CRP level, partial Mayo score (UC only) or HBI score (CD only), IBDQ score, SF-36 score, and EQ-5D score are summarized. The means of CRP level, partial Mayo score, and HBI score are plotted over time.

Table 6-2 describes the analyses for the exploratory efficacy objective.

Table 6-2 Summary of Analyses for Exploratory Objectives

Variable	Subpopulation	Analysis Type
CRP level	CD	Tabulate descriptive statistics for observed values and change from baseline
Partial Mayo Score	UC	Tabulate descriptive statistics for observed values and change from baseline
Partial Mayo Score	UC	Proportions of Partial Mayo score ≤ 2, 3 ≤ partial Mayo score ≤ 5 and partial Mayo score ≥ 6 over time
HBI Score	CD	Tabulate descriptive statistics for observed values and change from baseline
HBI Score	CD	Proportions of HBI score ≤ 4, 4 < HBI score ≤ 7 and HBI score > 7

Table 6-2 Summary of Analyses for Exploratory Objectives

Variable	Subpopulation	Analysis Type
CRP level	CD	Plot of mean observed values with 95% CI at each time point
Partial Mayo Score	UC	Plot of mean observed values with 95% CI at each time point
HBI Score	CD	Plot of mean observed values and with 95% CI at each time point

Abbreviations: CD = Crohn's disease; CI = confidence interval; CRP = C-reactive protein; HBI = Harvey-Bradshaw Index; UC = ulcerative colitis.

A comprehensive efficacy assessment for long-term clinical response and clinical remission as measured by partial Mayo score for UC and by HBI for CD will be covered by the integrated summary of efficacy that will have a separate analysis plan.

6.10 Resource Utilization Outcomes

Resources Utilization Outcomes collected in this study are as follows and are analyzed by CD or UC indication:

- Proportion of patients with CD-related hospitalization, bowel resection, or CD-related procedures(for CD patients)
- Proportion of patients with UC-related hospitalization, colectomies, or UC-related procedures (for UC patients)
- Time to CD-related hospitalization, bowel surgeries, or CD-related procedures (for CD patients)
- Proportion of patients with UC-related hospitalization, colectomies, or UC-related procedures (for CD patients)

For time-to-event analyses, Kaplan-Meier method is used for summarizing combined events.

Table 6-3 Summary of Analyses for Resource Utilization Objectives

Variable	Population	Analysis Type
Time to combined CD-related events	Efficacy population CD patients	Kaplan Meier estimates along with 95% CI at 52, 100, 148,196 weeks and continued at weeks by approximately 1 year until the final safety visit

Table 6-3 Summary of Analyses for Resource Utilization Objectives

Variable	Population	Analysis Type
Time to combined UC-related events	Efficacy population UC patients	Kaplan Meier estimates-along with 95% CI at 52, 100, 148, 196 weeks and continued at weeks by approximately 1 year until the final safety visit

Abbreviations: CD = Crohn's disease; CI = confidence interval; UC = ulcerative colitis.

6.11 Patient-Reported Outcomes (PROs)

Patient-reported outcomes on quality of life collected in this study are as follows:

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Short Form-36 (SF-36)
- EuroQol (EQ-5D)

Patient-reported outcomes are analyzed using the efficacy population. The baseline value is the last measurement before the first dose of vedolizumab from the previous study (C13006, C13007 or C13011) as defined in Section 5.2.

Summary tables for patient-reported outcomes such as IBDQ include baseline and each scheduled visit for the endpoint under consideration.

Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36, and EQ-5D are assessed at each scheduled visit. The mean changes from baseline in IBDQ total and subscale scores are presented along with 95% two-sided CIs for the differences in mean changes from baseline. In a similar manner, summaries of the changes from baseline in SF-36 summary scores physical component score (PCS) and mental component score (MCS), subscale scores, and EQ-5D utility and visual analogue scale (VAS) scores are provided.

Table 6-4 describes the tables and figures generated for the patient-reported outcomes objectives.

Table 6-4 Summary of Analyses for Patient-Reported Outcomes Objectives

Variable	Imputation	Analysis Type
IBDQ (total)	Efficacy Population	Changes from baseline at each scheduled visit, including mean and mean changes from baseline and 95% CI
IBDQ (subscales)	Efficacy Population	Changes from baseline at each scheduled visits, including mean and mean changes from baseline and 95% CI
SF-36 (PCS and MCS)	Efficacy Population	Changes from baseline at each scheduled visits, including mean and mean changes from baseline and 95% CI
SF-36 (subscales)	Efficacy Population	Changes from baseline at each scheduled visits, including mean and mean changes from baseline and 95% CI
EQ-5D Utility	Efficacy Population	Changes from baseline at each scheduled visits, including mean and mean changes from baseline and 95% CI
EQ-5D VAS	Efficacy Population	Changes from baseline at each scheduled visits, including mean and mean changes from baseline and 95% CI

7. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Patients who previously participated in the phase 2, open-label, long-term safety study (Study C13004) are part of the integrated safety analysis for Study C13008. Exposure, AE, and concomitant medication data from all patients who previously participated in Study C13004 are analyzed in Study C13008.

8. REFERENCES

1. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. December, 2004
2. Lachin, J.M., Biostatistical Methods, The Assessment of Relative Risks, 2000, *Wiley Serious in Probability and Statistics*

APPENDICES

APPENDIX 1 TABLES AND FIGURES

Tables and Figures will be provided upon request.

APPENDIX 2 LABORATORY ABNORMALITY CRITERIA

Table A2.1 provides the criteria for assessing marked abnormalities in safety laboratory parameters with thresholds based on grade 2 moderate intensity levels from the Division of AIDS table for grading the severity of adult and pediatric adverse events (December, 2004). As stated in Section 6.11.2.1, if both the baseline and on-treatment values of a parameter are beyond the same MA limit for that parameter, then the on-treatment value is considered a MA only if it is more extreme (farther from the limit) than was the baseline value.

Table A2.1: Marked Abnormality Criteria for Safety Laboratory Parameters

Parameter	Test Code	Units	Direction of Change	Marked Abnormalities
HEMATOLOGY				
Hemoglobin	HB	g/L	Low Only	≤ 70 g/L
Absolute Lymphocyte Count	LYMPH	10E9	Low Only	<0.5 X10E9
Leukocytes	WBC	10E9	Low Only	Absolute Value < 2.0X10E9
Platelets	PLT	10E9	Low Only	<75.0X10E9
Absolute Neutrophil Count	ANC	10E9	Low Only	<1.0X10E9
Prothrombin Time	PT	%	High Only	>1.25 x ULN
CHEMISTRIES				
SGPT	ALT	ULN	High Only	>3.0 x ULN
SGOT	AST	ULN	High Only	>3.0 x ULN
Bilirubin	BILI	ULN	High Only	>2.0 x ULN
Amylase	AMYL	ULN	High Only	>2.0 x ULN
Lipase	LIP	ULN	High Only	>2.0 x ULN
Serum Creatinine	CREAT	ULN	High Only	>2.0 x ULN

APPENDIX 3 GEOGRAPHIC REGIONS

Region	Countries		
North America	Canada	Puerto Rico	United States
Western/ Northern Europe	Austria France Ireland Norway Sweden	Belgium Germany Italy Portugal Switzerland	Denmark Iceland Netherlands Spain United Kingdom
Central Europe	Czech Republic Poland Slovak Republic	Greece Romania	Hungary Serbia
Eastern Europe	Bulgaria Latvia Turkey	Estonia Malta Ukraine	Israel Russia
Africa/Asia / Australia	Australia New Zealand Taiwan South Africa	Hong Kong South Korea China	India Malaysia Singapore

APPENDIX 4 MAYO SCORE CALCULATION WORKSHEET

Complete and Partial Mayo Scoring "Points to Remember"

The Mayo Score is widely used in clinical trials to assess Ulcerative Colitis disease activity. It is a combination of two patient-reported and two physician-determined components. The Partial Mayo Score includes only the Stool Frequency, Rectal Bleeding, and PGA subscores. (Does not include endoscopy)

Sub Scores

Stool Frequency (Patient) 0 = Normal number of stools for this patient 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal	Stool frequency WILL: ➢ Be derived from patient reported diary data in IVRS and will be the average of 3 days prior to visit ➢ Be variable from patient to patient. Instruct patients to set the baseline of "normal" to whatever is "normal" for them. (eg, A patient normally has 1 stool per day and today has had 4 stools. Therefore the patient has had 3 more than "normal", which yields a value of 2 for that day) ➢ Be defined as the passage of solid or liquid fecal material. Episodes of incontinence count. A non-productive trip to the bathroom or the simple passage of gas DO NOT COUNT as a stool.
Rectal Bleeding (Patient) 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes	Rectal bleeding WILL: ➢ Be derived from patient reported diary data in IVRS and will be the average of 3 days prior to visit ➢ Represent the most severe bleeding of the day. Hemorrhoidal bleeding DOES NOT COUNT.
Findings on Endoscopy (Physician) 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)	Findings on Endoscopy WILL: ➢ Be documented by photographic evidence ➢ Be classified by the worst affected segment if mucosal appearance varies ➢ Be characterized as follows • Moderate: Bleeds to touch (forceps applied to colonic mucosa for 1 second) • Severe: Bleeds spontaneously ➢ Endoscopy should be performed by the same endoscopist for any given patient
Physician's Global Assessment (Physician) 0 = Normal	Physician's Global Assessment WILL: ➢ Be based on the patient's overall status on the day of visit ➢ Reflect how the patient is doing at present. Assessment SHOULD NOT reflect past disease severity or complexity or the number/kinds of medications the patient is

1 = Mild disease 2 = Moderate disease 3 = Severe disease	receiving. ➢ Be based on the • Other 3 components of the Mayo score • Patient's recollection of abdominal discomfort and general sense of well-being • Patient's performance status, fecal incontinence, and mood • Physician's observations and physical exam findings ➢ Reflect disease activity, NOT disease severity (eg. Do not automatically give a high PGA to patients with pancolitis or severe/complicated disease, or patients requiring multiple medications.)
• Subscores representing the average of 3 days of patient diary data can be obtained from the IVRS subscore report. If calculated manually, subscores should be rounded to the nearest integer. • The Mayo score is equal to the sum of the subscores.	

APPENDIX 5 AES OF SPECIAL INTEREST

- Gastrointestinal Events
    - Use SOC of GASTROINTESTINAL DISORDERS to flag
- Malignancies
    - Use SOC of NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) to flag
- Infections
    - Use SOC of INFECTIONS AND INFESTATIONS to flag
- Infusion Related Reactions
    - Analysis for these AEs will occur on two levels:
        - Investigator defined Infusion Related Reactions (as indicated on the AE CRF)
        - All AEs that occur on or one calendar day after the infusion date.

APPENDIX 6 PRIOR THERAPIES

	Systemic Corticosteroids	Immunomodulators	Anti TNF
CRF Label	Systemic Corticosteroids	Azathioprine/ 6-Mercaptopurine	Infliximab
		Methotrexate	Adalimumab
			Certolizumab

APPENDIX 7 PATIENT REPORTED OUTCOMES

Table A7.1: Patient Reported Outcomes – IBDQ, SF-36 and EQ-5D

Variable		
SF-36	Sub-score	Calculation
	Physical Functioning (raw score)	Sum of (Q3a, Q3b,Q3c,Q3d,Q3e,Q3f,Q3g,Q3h, Q3i, Q3J)
	Role Physical (raw score)	Sum of (Q4a, Q4b, Q4c, Q4d)
	Bodily Pain (raw score)	Sum of (Q7,Q8)
	General Health (raw score)	Sum of (Q1, Q11a, Q11b, Q11c, Q11d)
	Vitality (raw score)	Sum of (Q9a, Q9e, Q9g, Q9i)
	Social Functioning (raw score)	Sum of (Q6, Q10)
	Role-Emotional (raw score)	Sum of (Q5a, Q5b, Q5c)
	Mental Health (raw score)	Sum of (Q9b,Q9c,Q9d,Q9f,Q9h)
Note	For each component score above, if 50% or less of the component score is missing at a visit, the MEAN of the remaining component score will be imputed as the value for the missing component score. If more than 50% of the component score is missing for the item, the imputed value will be set to missing.	
	Physical Functioning (S-score)	(PF score -10)/20*100
	Role Physical (S- score)	(RP score -4)/16*100
	Bodily Pain (S- score)	(BP score-2)/10*100
	General Health (S- score)	(GH score -5)/20*100
	Vitality (S- score)	(VT score -4)/16*100
	Social Functioning (S-score)	(SF score -2)/8*100
	Role-Emotional (S- score)	(RE score -3)/12*100
	Mental Health (S- score)	(MH score -5)/20*100
	Physical Functioning (Z-score*)	(PF – 83.29094)/23.75883
	Role Physical (Z-score)	(RP-82.50964)/25.52028
	Bodily Pain (Z-score)	(BP-71.32527)/23.66224
	General Health (Z-score)	(GH-70.84570)/20.97821
	Vitality (Z-score)	(VT-58.31411)/20.01923
	Social Functioning (Z-score)	(SF-84.30250)/22.91921
	Role-Emotional (Z-score)	(RE-87.39733)/21.43778

Table A7.1: Patient Reported Outcomes – IBDQ, SF-36 and EQ-5D		
Variable		
	Mental Health (Z-score)	(MH-74.98685)/17.75604
	Aggregated physical score	PHYS = (PF_Z*0.42402) + (RP_Z*0.35119) +(BP_Z*0.31754)+(GH_Z*0.24954)+(VT_Z*0.02877) +(SF_Z*0.00753*(-1))+(RE_Z* 0.19206*(-1)) + (MH_Z*0.22069*(-1))
	Aggregated Mental score	MENT = (PF_Z*0.22999*(-1)) + (RP_Z*0.12329* (-1)) +(BP_Z*0.09731*(-1))+(GH_Z*0.01571*(-1))+ (VT_Z*0.23534) +(SF_Z*0.26876)+(RE_Z* 0.43407) + (MH_Z*0.48581)
Note	If less than or equal to 4 Z-scores are missing, the average of the remaining Z scores will be used to compute the value for the missing component score. If more than 4 Z scores are missing, the aggregate mental or physical will be set to missing.	
IBDQ	Sub-score	Calculation
	IBDQ Bowel symptoms score	Sum of (Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, Q29), Ranging from 10 to 70, 10 questions
	IBDQ Emotional function score	Sum of (Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31, Q32), Ranging from 12 to 84, 12 questions
	IBDQ Social function score	Sum of (Q4, Q8, Q12, Q16,Q28), Ranging from 5 to 35, 5 questions
	IBDQ Systemic symptoms score	Sum of (Q2, Q6, Q10, Q14,Q18), Ranging from 5 to 35, 5 questions
Note	For each component score above, if 50% or less of the component score is missing at a visit, the MEAN of the remaining component score will be imputed as the value for the missing component score. If more than 50% of the component score is missing for the item, the imputed value will be set to missing.	
	IBDQ score	Sum of (bowel, emotion, social, system)
Note	If any of the component score is missing at a visit, the imputed value will be set to missing..	
EQ-5D	Sub-score	Calculation
	EQ5D Mobility component score	Ranging from 1 to 3
	EQ5D self-care component score	Ranging from 1 to 3
	EQ5D usual activities component score	Ranging from 1 to 3
	EQ5D Pain/discomfort	Ranging from 1 to 3

Table A7.1: Patient Reported Outcomes – IBDQ, SF-36 and EQ-5D		
Variable		
	component score	
	EQ5D anxiety/depression component score	Ranging from 1 to 3
Note	If 2 or less out of 5 of the components are missing at a visit, the MEAN of the remaining component score will be imputed as the value for the missing component score. If 3 or more components are missing, the imputed value will be set to missing.	
EQ5D VAS	On a scale of 0 to 100, where 0 is the worst imaginable health state and 100 is the best imaginable health state.	

* Z-scores formula are described in the SC-36 Manual

APPENDIX 8 AES OF SPECIAL INTEREST

Infections
Bacterial pneumonia
Bacteremia
Sepsis
Pneumocystis jiroveci (carinii) pneumonia
Pyelonephritis
Herpes zoster
Progressive multifocal leukoencephalopathy
Tuberculosis
Histoplasmosis
Listeria meningitis
Mycobacteria avium complex
Candidiasis
Herpes simplex
Dental abscesses/periodontitis
Rectal or peritoneal abscesses
Salmonella septicemia
Cryptosporidiosis
C. difficile diarrhea/colitis
CMV colitis
Urinary tract infection
Giardiasis
Cellulitis
Viral meningitis
Cancer
All primary solid tumors
Lymphatic and hematopoietic malignancies
Lymphosarcoma and reticulosarcoma
Marginal zone lymphoma
Hodgkin's disease
Other malignant neoplasms of lymphoid and histiocytic tissue
Peripheral t-cell lymphoma
Multiple myeloma and immunoproliferative neoplasms
Lymphoid leukemia
Myeloid leukemia
Monocytic leukemia
Other leukemia
Digestive tract
Oropharyngeal

Esophagus
Stomach
Small intestine
Colon
Rectum, anus
Intrahepatic bile ducts
Gall bladder
Pancreas
Retroperitoneum and peritoneum
Other
Cervical carcinoma
Melanoma
B-cell lymphoma
Cervical dysplasia
Gastrointestinal
Intestinal obstruction/stenosis
Abdominal abscesses
Abscess of anal and rectal regions
Campylobacter gastroenteritis
Salmonella gastroenteritis
Viral gastroenteritis
Intestinal/gastric perforation
Miscellaneous
Deep venous thrombophlebitis
Pulmonary embolus
Stroke
Congestive heart failure and/or Stevens-Johnson syndrome/toxic epidermal necrolysis
Erythema multiforme
Stevens-Johnson syndrome/Toxic epidermal necrolysis
Acute myocardial infarction
Kidney stones
Acute renal failure/renal insufficiency (excluding chronic)
Angioedema