Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study, with a vedolizumab IV Reference Arm, to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

NCT Number: NCT02611830

SAP Approve Date: 2 June 2018

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: MLN0002SC-3027

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study, with a vedolizumab IV Reference Arm, to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

PHASE 3

Version**:** 1.0

Date**: 1**2 June 2018

Prepared by:

PPD

Based on:

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Protocol Date: <26 July 2016>

1.1 APPROVAL SIGNATURES

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AESI	adverse event of special interest
AVA	anti-vedolizumab antibody; also called HAHA
CMH	Cochran-Mantel-Haenszel
C_{trough}	trough serum concentration
ECG	electrocardiogram
ECL	Electrochemiluminescence
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EQ-5D	Euro Quality of Life-5D
FAS	full analysis set
HLT	high level term
IBDQ	Inflammatory Bowel Disease Questionnaire
IV	intravenous(ly)
KM	Kaplan-Meier
LTFU	long-term follow-up
MAR	Missing at random
MAV	markedly abnormal laboratory value
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at random
OLE	open-label extension
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPS	per-protocol set
PRO	patient-reported outcome
PT	preferred term
Q2W	once every 2 weeks
Q8W	once every 8 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SI	Systeme International
TB	tuberculosis
TEAE	treatment-emergent adverse event
TRAE	treatment related AE
TNF-α	tumor necrosis factor- alpha
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale

Term	Definition
WHODRUG	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

4.0 OBJECTIVES

4.1 Primary Objectives

To assess the effect of vedolizumab subcutaneous (SC) maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active ulcerative colitis (UC) who achieved clinical response at Week 6 following administration of vedolizumab intravenous (IV) at Weeks 0 and 2.

4.2 Secondary Objectives

- To determine the effect of vedolizumab SC maintenance treatment on mucosal healing at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on durable clinical response at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on durable clinical remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on corticosteroid-free remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

4.3 Exploratory Objectives

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4.4 Study Design

This is a pivotal, phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled trial, including a vedolizumab IV reference arm, designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active UC who achieved a clinical response at Week 6 with open-label therapy with 300 mg vedolizumab IV at Weeks 0 and 2. The study includes a vedolizumab IV reference arm to allow for within-study descriptive comparisons on efficacy, safety, and immunogenicity between the two vedolizumab presentations.

The study includes a 4-week (28-day) Screening Period, a 6-week open-label vedolizumab IV Induction Phase, and a 46-week randomized, double-blind, double-dummy, placebo-controlled Maintenance Phase with vedolizumab SC or vedolizumab IV with a final visit at Week 52. All endoscopic assessments (ie, for disease severity at baseline and for clinical endpoints at the end of the Induction and Maintenance Phases) will be performed via central reading.

Eligible subjects, will be enrolled into the Induction Phase at Week 0, will receive open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2, and will be assessed for clinical response by full Mayo score (endoscopy score determined by central reading) at Week 6, as follows:

- Subjects who achieve a clinical response at Week 6 will be randomized into the Maintenance Phase. Upon completion of the Week 52 assessment or upon early discontinuation due to treatment failure (ie, disease worsening or need for rescue medications) these subjects will be eligible to enter the MLN0002SC-3030 open-label extension (OLE) study.
- Subjects who do not achieve a clinical response at Week 6 will not be randomized in to the Maintenance Phase, and instead will receive a third infusion of vedolizumab IV 300 mg at Week 6. Subjects who achieve a clinical response at Week 14 (by partial Mayo score) will be eligible to enroll in the OLE study, while subjects who do not achieve clinical response will be discontinued.

Subjects with clinical response at Week 6 will be randomized at a 2:1:1 ratio in the double-blind, double-dummy Maintenance Phase, where each treatment arm will receive both SC injections Q2W and IV infusions Q8W, beginning at Week 6 through Week 50, as follows:

- Injections of vedolizumab SC 108 mg Q2W and placebo IV infusions every 8 weeks (Q8W) (N=94).
- Infusions of vedolizumab IV 300 mg Q8W and placebo SC injections Q2W (N=47).
- Placebo SC injections Q2W and placebo IV infusions Q8W (N=47).

Randomization will be stratified by:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF-α antagonists failure or concomitant immunomodulator (azathioprine or 6-mercaptopurine) use.

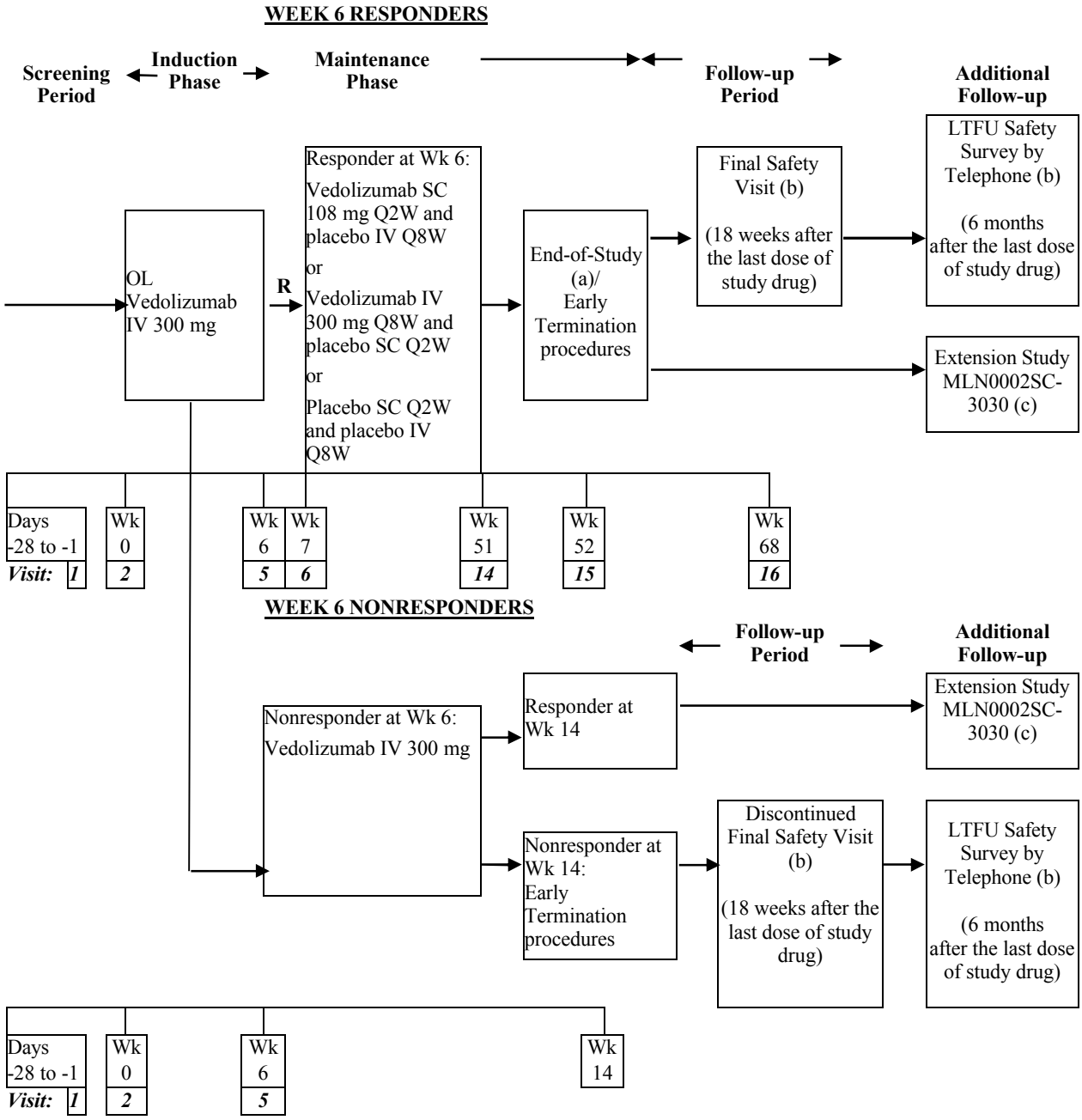
At Week 6, subjects receiving oral corticosteroids who achieved a clinical response and are randomized into the Maintenance Phase will begin a corticosteroid tapering regimen.

Subjects who do not participate in the OLE trial or are discontinued, will complete the End-of-Study Visits or Early Termination visit and then complete the Final Safety Visit 18 weeks (ie, 5 vedolizumab half-lives) after the last dose of study drug. For subjects that are not in response at Week 14, early termination procedures will be performed at the Week 14 visit.

Additionally, subjects who do not participate in the OLE trial will be required to participate in a long-term follow-up (LTFU) safety-survey by telephone, 6 months after the last dose of study drug.

A schematic of the study design is included as Figure 4.a. A schedule of assessments is listed in Appendix A of protocol.

Figure 4.a Schematic of Study Design



OL=open-label, R=randomization.
(a) Subjects who consent to participate in the extension study (MLN0002-3030) may begin extension study dosing after End-of-Study Visit procedures have been completed at the Week 52 Visit.
(b) Subjects who do not enter the extension study (MLN0002SC-3030) (including early terminators and Week 14 nonresponders) will complete the Final Safety Visit 18 weeks after their last dose of study drug and participate in a Follow-up Safety Survey by Telephone 6 months after the last dose of study drug.
(c) Visit 1 of Extension Study MLN0002SC-3030 is within 1 week of completing Week 52 (Visit 15) procedures. Subjects not randomized into the Maintenance Phase (Week 6 Nonresponders) and respond at Week 14 on vedolizumab IV 300 mg are also eligible for entry into the Extension Study.

5.0 ANALYSIS ENDPOINTS

The endpoints pertain to the vedolizumab SC and placebo arms only.

5.1 Primary Endpoint

- Proportion of subjects with clinical remission, defined as a complete Mayo score of ≤2 points and no individual subscore >1 point, at Week 52.

5.2 Secondary Endpoints

- Proportion of subjects with mucosal healing, defined as Mayo endoscopic subscore of ≤1 point, at Week 52.
- Proportion of subjects with durable clinical response, defined as clinical response at Weeks 6 and 52, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
- Proportion of subjects with durable clinical remission, defined as clinical remission at Weeks 6 and 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.

5.3 Patient Reported Outcome (PRO) Endpoints

- Changes in Inflammatory Bowel Disease Questionnaire (IBDQ) total score and subscores, from Baseline (Week 0) to Week 52 and from Week 6 to Week 52.
- Changes in Euro Quality of Life-5D (EQ-5D) utility scores and EQ-5D VAS score from Baseline (Week 0) to Week 52 and Week 6 to Week 52.
- Changes in WPAI-UC instrument endpoints (% work time missed, % impairment while working, % overall work impairment, % activity impairment) from Baseline (Week 0) to Week 52 and Week 6 to Week 52.

5.4 Exploratory Endpoints

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5.4.1 Additional Exploratory Endpoints

Following endpoints are not specified in the protocol but will be added to the final analysis.

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[redacted]

5.5 Safety Assessments

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs) (including serious infections including opportunistic infection such as progressive multifocal leukoencephalopathy (PML), liver injury, malignancies, infusion-related or injection site reactions or systemic reactions and hypersensitivity), serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and results of 12-lead electrocardiograms (ECGs).

6.0 DETERMINATION OF SAMPLE SIZE

Assuming a clinical remission rate of 42% for vedolizumab and 16% for placebo at Week 52, a sample size of 94 subjects in the vedolizumab SC group and 47 subjects in the placebo group will provide 90% power at a 2-sided 0.05 level of significance. To ensure a randomized sample size of 188 subjects, assuming 47% of the subjects entering induction will achieve clinical response at Week 6, approximately 400 subjects will need to be enrolled into the study.

Assuming a mucosal healing rate of 52% for vedolizumab and 20% for placebo at Week 52, with a sample size of 94 subjects in the vedolizumab group and 47 subjects in the placebo group the first secondary endpoint of mucosal healing at Week 52 will be powered to at least 97% at a 2-sided 0.05 level of significance.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

Statistical analysis will be performed using the SAS System, Version 9.2 or higher.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. Continuous data will be summarized using number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

7.1.1 Study Terms and Definitions

Term	Definition
Clinical remission by complete Mayo score	A complete Mayo score of ≤2 points and no individual subscore >1 point.
Clinical remission by partial Mayo score	A partial Mayo Score ≤2 and no individual subscore >1.
CCI	[redacted]
Clinical response	A reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Week 0) (or partial Mayo score of ≥2 points and ≥25% from Baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
Corticosteroid-free remission	Defined as proportion of subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
Disease worsening	An increase in partial Mayo score ≥3 points from the Week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 6 value >6) and a minimum partial Mayo score of ≥5 points.
Durable clinical remission	Clinical remission at Weeks 6 and 52.
Durable clinical response	Clinical response at Weeks 6 and 52.
Mucosal healing	A Mayo endoscopic subscore of ≤1 point.
CCI	[redacted]

7.1.2 Convention for Calculations of Mayo Scores

7.1.2.1 Gemini Approach

Primary method for calculation of Mayo Scores will be followed by the same approach used in Gemini study (MLN0002 C13006). Statistical programming will calculate the Mayo score and Partial Mayo score for each subject. The Mayo scoring system is a composite index of 4 disease activity variables. Each variable is scored individually on an integer scale of 0 to 3, with higher scores indicating greater disease activity. The individual components of the Mayo score are stool frequency, rectal bleeding, findings on sigmoidoscopy, and the physician's global assessment. The Partial Mayo score is calculated analogously but excludes the sigmoidoscopy subscore. Mayo score calculation "points to remember" are in Appendix C.

Stool frequency and rectal bleeding subscores are derived from eDiaries completed by the subject seven days prior to a study visit. These subscores are calculated using the eDiary in the following order:

- The score from the 3 most recent days prior to the actual day of the study visit will be averaged and rounded to the nearest integer.
- If diary entries from 3 days are not available, the scores from the 2 most recent entries will be averaged and rounded to the nearest integer.
- If less than 2 days of diary data are available, the patient will be categorized as a non-responder and the subscore will be considered missing.

The day of sigmoidoscopy must be entered into eDiary (not applicable at all study visits), and day of visit must be confirmed in eDiary. Table 7.a provides examples of Mayo subscore calculation using various eDiary scenarios (eligibility only); Table 7.b provides examples of Mayo subscore calculation using various eDiary scenarios (excluding eligibility).

Subjects who have less than 3 days of diary data during screening are not eligible for enrollment (ie, for eligibility, only Rule #1 will be applied). During screening, subjects should have 3 non-missing diary out of 7 days immediately prior to eligibility visit so that they are eligible for score calculation (see example Diary# 5 and 6 in Table 7.a).

The day prior, day of, and day after sigmoidoscopy cannot be used for subject diary entry because of the bowel prep for the procedure could interfere with the assessment of these clinical parameters entered into eDiary.

Table 7.a Example of eDiary Subscore Calculations for Eligibility Visit

Example	Day(a) -10	Day -9	Day -8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 1	Valid Days for Calculation of Subscore	Average Subscore	Final Subscore
Diary #1	1	3	2	X	S	X	2	3	0	1	E	-1, -2, -3	1.33	1
Diary #2	2	3	2	3	X	S	X	1	M	2	E	-1. -3, -7	2	2
Diary #3	1	2	3	2	3	4	4	3	4	X	S & E	-2, -3, -4	3.67	4
Diary #4	4	3	4	4	4	X	S&E	X				-6, -7, -8	4	4
Diary #5	2	2	X	S & E	X							Not eligible	NA	M
Diary #6	2	4	2	3	3	X	S	X	M	M	E	Not eligible	NA	M

NA=not applicable.
(a) Days are named relative to Day 1, which is the first dose date. Subject diaries can be completed 10 days prior to eligibility visit.
S=sigmoidoscopy.
X=the score can't be counted to prior or after sigmoidoscopy.
E=eligibility visit.
M=missing.

Table 7.b Example of eDiary Subscore Calculations for Non-eligibility Visits

Example	Day(a) -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Valid Days for Calculation of Subscore	Average Subscore	Final Subscore
Diary #1	X	S	X	2	3	0	1	-1, -2, -3	1.33	1
Diary #2	3	X	S	X	1	M	2	-1. -3, -7	2	2
Diary #3	S	X	3	M	M	M	0	-1, -5	1.5	2
Diary #4	4	4	X	S	X	3	3	-1, -2, -6	3.33	3
Diary #5	2	3	4	4	X	S	X	-4, -5, -6	3.67	4
Diary #6	2	M	M	X	S	X	2	-1, -7	2	2
Diary #7	M	3	X	S	X	M	M	M	NA	M

NA=not applicable.
(a) Days are named relative to Day 1, which is the study visit.
S=sigmoidoscopy.
X=the score can't be counted to prior or after sigmoidoscopy.
M=missing.

7.1.2.2 FDA Guided Approach

As a sensitivity analysis, the complete Mayo score and partial Mayo score for each patient will be calculated for post-screening visit per FDA Draft Ulcerative Colitis guidance (August 2016). For post-screening visits, the stool frequency and rectal bleeding subscores will be calculated as the sum of the 3 most recent consecutive non-missing results divided by 3. For patients who do not have 3 consecutive days of non-missing eDiary data but have at least 4 days of data available in the last 7-day period prior to the visit, the non-missing scores from the total number of available days in the last 7-day period will be averaged. If less than 3 consecutive days or 4 days

of eDiary data in the last 7-day period are available, the patient will be categorized as a non-responder and the subscore will be considered missing.

7.1.3 Duplicate Records due to Patient Self-Entered Data

SC dosing done during mandatory site visits will be recorded into the eCRF. If patients accidentally recorded SC dosing done during site visits on the same day of clinic visit, data recorded on eCRF will be used;

If patients have multiple entries on the same day for either stool frequency or rectal bleeding, the worst results will be used for Mayo score calculation. If patients entered for "previous day" but have already entered the record one day before, the one entered for "previous day" will be ignored.

7.1.4 Convention for missing data

- Missing data for dichotomous (i.e., proportion-based) endpoints will be handled using the non-responder imputation method, i.e. any subject with missing information for determination of endpoint status will be considered as a non-responder in the analysis.

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- Missing data for continuous endpoints will be imputed using last available post-baseline observation carried forward (LOCF) method. For subjects without any non-missing post-baseline measurement, the missing data will be imputed using baseline observation carried forward method. Other missing data imputation method may be explored.

7.1.5 Definition of Study Days and Visit Window

Study day will be calculated relative to the date of the first dose of study drug (first dose of IV infusion) in the study. The study day prior to the first dose of study drug will be calculated as:

Date of assessment/event – date of first dose of study drug.

The study day on or after the first dose of study drug will be calculated as:

Date of assessment/event – date of first dose of study drug + 1.

Baseline is defined as the last non-missing measurement prior to or on the date of the first dose of study drug (Study Day 1). The visit windows for the postbaseline visits are defined in Table 7.c and Table 7.d. If a subject has more than 1 measurement in the same visit window, the measurement closest to the scheduled visit will be used. If 2 measurements in the same window are of equal distance to the scheduled visit, the measurement that occurs after the scheduled visit will be used. If 2 or more measurements occur on the same day, the last value obtained will be used.

AEs that start more than 127 days after the last dose of study drug will be listed, but excluded from the summaries and analyses.

If Endoscopy is taken other than protocol defined visits (baseline, week 6, or week 52), i.e. at early termination (ET), then the visit window for endoscopy will follow the one of partial Mayo Score, and the subject's complete Mayo score at the corresponding protocol defined visits (i.e. week 6 or week 52) will be set to missing with one exception. If week 52 complete MAYO is missing, week 50 complete MAYO, if available, will be carried over.

Table 7.c Visit Windows (Induction Period for Non-responders at Week 6)

Visit	Scheduled Day	Safety Labs	Vital Signs	Urinalysis	Partial Mayo Score, Corticosteroide	Endoscopy	IBDQ, EQ-5D, WPAI-UC
Baseline	Day 1	≤1	≤1	≤1	≤1	≤1	≤1
Week 2	Day 14	2-28	2-28	2-28	NA	NA	NA
Week 6	Day 42	29-70	29-70	≥29	2-70	2-70	2-70
Week 14[*a] [*b]	Day 98	71-133	71-133	NA	71-133	NA	NA
Week 24[*c]	Day 168	≥134	≥134	NA	NA	NA	NA

*[a] Week 14 will end on Day 133 or the day prior to the first dosing of the extension study (for patients entering the extension study), whichever comes first.

*[b] For the purpose of diary compliance calculation and derivation of diary-based endpoints, the last visit day of study will not be included since the subject is not expected to have completed the diary entries for that day by the Final Visit.

*[c] Safety follow up visit. Only for subjects who do not enter the Extension Study MLN002SC-3030 (including early terminators and Week 14 non-responders).

Table 7.d Visit Windows (Randomized Subjects)

Visit	Scheduled Day	Safety Labs	Vital Signs	ECG	Urinalysis	Partial Mayo Score, Corticosteroide	Endoscopy	IBDQ, EQ-5D, WPAI-UC
Baseline	Day 1	≤1	≤1	≤1	≤1	≤1	≤1	≤1
Week 2	Day 14	2-28	2-28	NA	2-28	NA	NA	NA
Week 6	Day 42	29-70	29-70	NA	29-70	2-70	2-70	2-70
Week 14	Day 98	71-126	71-126	NA	NA	71-126	NA	NA
Week 22	Day 154	127-182	127-182	NA	NA	127-182	NA	NA
Week 30	Day 210	183-238	183-238	NA	NA	183-238	NA	71-238
Week 38	Day 266	239-294	239-294	NA	NA	239-294	NA	NA
Week 46	Day 322	295-336	295-336	NA	NA	295-336	NA	NA
Week 50	Day 350	337-357	337-357	NA	NA	337-357	NA	NA
Week 52	Day 364	358-420	358-420	≥2	≥71	≥358	≥71	≥239
Week 68*	Day 476	≥ 421	≥ 421	NA	NA	NA	NA	NA

* Safety follow up visit. Only for subjects who do not enter the Extension Study MLN002SC-3030.

7.2 Analysis Sets

7.2.1 Full Analysis Set (FAS)

The FAS will include all randomized subjects who receive at least 1 dose of study drug. Subjects who only receive induction IV therapy and not randomized into the maintenance phase will not be included in the FAS. Subjects in this set will be analyzed according to the treatment they were randomized to receive.

The FAS will be used for the efficacy analysis with exception of corticosteroid-free remission, which will be based on a subset of the FAS subjects with baseline concomitant oral corticosteroid use.

7.2.2 Per-Protocol Set (PPS)

The PPS is a subset of the FAS. The PPS consists of all subjects who do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects for the PPS dataset will be made prior to the unblinding of the study. Additional exclusion from the PPS may be finalized as part of a final data review and documented prior to database lock.

Analyses using the PPS may be provided as a sensitivity analysis.

7.2.3 Safety Analysis Set

The Safety Analysis Set (SAF) will include all subjects who receive at least 1 dose of study SC (placebo or vedolizumab) drug. Subjects in this set will be analyzed according to the treatment that was actually received. SAF-I will include all subjects who receive at least 1 induction dose, but were not randomized to maintenance phase. SAF-C will include all subjects who receive at least 1 dose of vedolizumab IV.

7.2.4 Pharmacokinetic Set

The PK evaluable population is defined as all subjects who receive at least 1 dose of study SC (placebo or vedolizumab) drug and have sufficient blood sampling to allow for PK evaluation. PK-C will include all subjects who receive at least 1 dose of vedolizumab IV and have sufficient blood sampling to allow for PK evaluation. PK-I is all subjects who receive at least 1 induction dose but were not randomized into maintenance phase, with sufficient blood sampling to allow for PK evaluation.

7.3 Disposition of Subjects

A subject disposition summary will be provided. Subjects' study completion data, including reasons for premature termination, will be provided in listings and be summarized. Significant protocol deviations captured on the electronic case report form (eCRF) will be summarized. A summary of screening failures will also be provided.

7.4 Demographic and Baseline Characteristics

Demographic variables will be summarized for the SAF-C. If the actual treatment of any patient is different from the randomized treatment, the demographic variables will also be summarized for the FAS.

For continuous variables (age, weight, height, and body mass index [BMI]), summary statistics will be generated. BMI (in kg/m^2) will be calculated using the subject's baseline height and weight measurements and summarized. For categorical variables, the number and percentage of subjects in each category will be presented.

The following UC-related baseline characteristics will be summarized for subjects in the FAS:

- Duration of UC (<1 year, ≥1 to <3 years, ≥3 to <7 years, ≥7 years).
- Subjects without concomitant corticosteroids or immunomodulators.
- Subjects with only concomitant corticosteroids.
- Subjects with only concomitant immunomodulators.
- Subjects with concomitant corticosteroids and immunomodulators.
- Subjects with prior tumor necrosis factor-alpha (TNF-α) antagonist use.
- Subjects with prior immunomodulator and prior TNF-α antagonist failure.
- Worst prior treatment failure (subjects with prior TNF-α anatomist failure, subjects with prior immunomodulator failure, subjects with prior corticosteroid failure).
- Baseline disease activity (baseline Mayo score: Mild <6, moderate=6 to 8, severe=9 to 12).
- Baseline fecal calprotectin (≤250 μg/g, >250 to ≤500 μg/g, >500 μg/g).
- Disease localization (proctosigmoiditis, left-sided colitis, extensive colitis, or pancolitis).
- Smoking status.
- Extraintestinal manifestations.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be presented in a data listing and will be summarized for the SAF.

7.6 Medication History and Concomitant Medications and Procedures

All medication history and concomitant medications will be coded by therapeutic classification, subclassification, and medication using the World Health Organization Drug Dictionary (WHODrug). A concomitant medication is defined as a medication that is ongoing as of Study Day 1, ends on or after Study Day 1, or starts on or after Study Day 1 and no more than 127 days after the last dose of study drug.

The number and percentage of subjects taking each concomitant medication during the induction phase and 46-week maintenance phase will be summarized for the SAF. Additional summary will be for SAF-I during the induction phase. A subject with 1 or more concomitant medications within the same level of the WHODrug classification will be counted only once in that level. WHODrug preferred term and therapeutic classification will be used for summary:

- Medication history that the study subjects stopped taking within 30 days prior to the Screening Visit.
- Concomitant medications that started and stopped prior to Baseline.
- Concomitant medications that started prior to and were ongoing at Baseline.
- Concomitant medications that started after Baseline.
- Concomitant medications that were ongoing at Baseline and those that started after Baseline.

Concomitant procedures will not be coded, but will be presented in listings for each subject.

7.7 Study Drug Exposure and Compliance

Overall study drug compliance (%) will be determined as (total count of complete injections or infusions taken / total number of injections or infusions expected during study treatment) × 100%. A subject must receive at least 75% of the infusion in order for it to be considered complete for each dose.

The total number of days on study drug (exposure) will be calculated as (date of last dose of study drug - date of first dose of study drug) + 127 days. Any gaps in dosing will be ignored when calculating the total. If last dose date is missing, then 127 days will be imputed as treatment period. Summary statistics for the total number of days on study drug and overall compliance will be generated for the SAF.

The number and percentage of subjects with overall study drug compliance of <80%, 80 to <90%, and ≥90% will also be summarized for the SAF. Subjects with unreturned study drug will be assumed to have injected study drug Q2W for each 2 weeks of exposure for the calculation of overall compliance. Subjects with overall compliance ≥100% will be set to 100% in the analysis.

In addition, diary compliance will be determined as the percentage of days during treatment with a diary entry:

> Diary Compliance =
> (Number of days with diary entries collected during treatment period)/(Number of days with diary entries expected during treatment period) × 100%

7.8 Efficacy Analysis

The FAS will be used for the summary of the efficacy endpoints with exception of corticosteroid-free remission, which will be based on a subset of FAS subjects with baseline concomitant oral corticosteroid use.

7.8.1 Primary Efficacy Endpoint

The primary endpoint is proportion of subjects with clinical remission, defined as a complete Mayo score of ≤2 points and no individual subscore >1 point, at Week 52.

The null and alternative hypotheses for the primary efficacy endpoint, clinical remission at Week 52, are:

H_0: Clinical Remission $_{\text{Vedolizumab SC}}$ at Week 52 = Clinical Remission $_{\text{Placebo}}$ at Week 52

versus

H_A: Clinical Remission $_{\text{Vedolizumab SC}}$ at Week 52 ≠ Clinical Remission $_{\text{Placebo}}$ at Week 52

Clinical remission at Week 52 will be analyzed in the FAS using Cochran-Mantel-Haenszel (CMH) tests stratified by randomization stratification factors according to:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF-α antagonists failure or concomitant immunomodulator (azathioprine or 6-mercaptopurine) use.

Descriptive statistics will be presented by treatment group. Count, percentage and associated 95% CI using the Clopper-Pearson method will be provided for each treatment group. The statistical significant treatment effect will be tested against 2-sided alpha level of 0.05. The p-value and point estimate of treatment difference based on the CMH method adjusted for stratification factors along with 95% confidence interval will be presented. The absolute treatment difference based on crude estimates with 95% CI using the normal approximation method will be displayed as well. If the number of remissions is too small (e.g., ≤ 5), the exact method (e.g., Fisher's Exact test and exact unconditional confidence limits) will be performed instead. All subjects with missing data for determination of clinical remission at Week 52 will be considered as non-remitters in the analysis.

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[redacted]

7.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects with mucosal healing, defined as Mayo endoscopic subscore of ≤1 point, at Week 52.
- Proportion of subjects with durable clinical response, defined as clinical response at Weeks 6 and 52, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

- Proportion of subjects with durable clinical remission, defined as clinical remission based on complete Mayo score at Weeks 6 and 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission based on complete Mayo score at Week 52.

Mucosal healing at Week 52, durable clinical response and durable clinical remission will be analyzed for the FAS subjects. Corticosteroid-free remission at Week 52 will be analyzed in a subset of the FAS subjects with baseline concomitant oral corticosteroid use. All secondary endpoints will be analyzed using CMH tests for risk differences, stratified by randomization stratification factors. The descriptive statistics will be presented for each of the secondary endpoints in a similar way to the primary endpoint.

The null and alternative hypotheses for the first secondary efficacy endpoint, mucosal healing at Week 52, are:

$$H_0: \text{Mucosal Healing}_{\text{Vedolizumab SC}} \text{ at Week 52} = \text{Mucosal Healing}_{\text{Placebo}} \text{ at Week 52}$$

versus

$$H_A: \text{Mucosal Healing}_{\text{Vedolizumab SC}} \text{ at Week 52} \neq \text{Mucosal Healing}_{\text{Placebo}} \text{ at Week 52}$$

The null and alternative hypotheses for the second secondary efficacy endpoint, durable clinical response at Week 6 and 52, are:

$$H_0: \text{Durable Clinical Response}_{\text{Vedolizumab SC}} \text{ at Week 52} = \text{Durable Clinical Response}_{\text{Placebo}} \text{ at Week 52}$$

versus

$$H_A: \text{Durable Clinical Response}_{\text{Vedolizumab SC}} \text{ at Week 52} \neq \text{Durable Clinical Response}_{\text{Placebo}} \text{ at Week 52}$$

The null and alternative hypotheses for the third secondary efficacy endpoint, durable clinical remission at Week 6 and 52, are:

$$H_0: \text{Durable Clinical Remission}_{\text{Vedolizumab SC}} \text{ at Week 52} = \text{Durable Clinical Remission}_{\text{Placebo}} \text{ at Week 52}$$

versus

$$H_A: \text{Durable Clinical Remission}_{\text{Vedolizumab SC}} \text{ at Week 52} \neq \text{Durable Clinical Remission}_{\text{Placebo}} \text{ at Week 52}$$

The null and alternative hypotheses for the fourth secondary efficacy endpoint, corticosteroid-free remission at Week 52, are:

$$H_0: \text{Corticosteroid-free Remission}_{\text{Vedolizumab SC}} \text{ at Week 52} = \text{Corticosteroid-free Remission}_{\text{Placebo}} \text{ at Week 52}$$

versus

H_A: Corticosteroid-free Remission $_{\text{Vedolizumab SC}}$ at Week 52 ≠ Corticosteroid-free Remission $_{\text{Placebo}}$ at Week 52

To control the overall Type I error rate for the comparison between vedolizumab SC and placebo groups for the primary and secondary endpoints, a hierarchical approach will be applied to the statistical testing of the secondary endpoints. The statistical inference for the first secondary endpoint of mucosal healing will only be performed if the primary endpoint, proportion of subjects with clinical remission at Week 52, is statistically significant ($p < 0.05$). The second secondary endpoint of durable clinical response will only be tested if the first secondary endpoint is statistically significant ($p < 0.05$). Similarly, the third secondary endpoint of durable clinical remission will only be tested if the second secondary endpoint is statistically significant ($p < 0.05$), and the fourth secondary endpoint of corticosteroids-free clinical remission will only be tested if the third secondary endpoint is statistically significant ($p < 0.05$).

Secondary efficacy endpoints will be analyzed in a similar way to the primary efficacy endpoint. The descriptive statistics of treatment effects and corresponding 95% CIs for the vedolizumab IV arm versus placebo for each of the secondary endpoints will be presented. The exact method will be performed if the number of observations is too small (e.g., ≤ 5).

7.8.3 Patient Reported Outcomes (PROs) Endpoints

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[redacted]

7.8.4 Exploratory and additional Efficacy Endpoints

CCI

[redacted]

7.8.5 Subgroup Analysis

Descriptive analyses will be performed on the primary and all secondary endpoints to summarize the treatment effects across subpopulations. The treatment effect in proportions in Vedolizumab

SC and placebo and associated 95% confidence interval using Clopper-Pearson method will be provided for each subgroup. Point estimate of the absolute treatment difference between Vedolizumab SC and placebo based on crude estimate and associated 95% confidence interval (using normal approximation method) will be presented. If the number of events is too small (ie, ≤ 5), the exact method will be performed instead. The results will be tabulated and the corresponding forest plots for the subgroup analyses will be presented as well.

For subgroup analysis by prior use of anti-TNFα antagonist only, nominal p-value will be obtained by the CMH test stratifying by baseline concomitant use of oral corticosteroids (Yes/No) and remission status at week 6 (Yes/No), or Fisher's exact test in the event of small number responders (ie, ≤ 5).

If the value of the baseline grouping variable cannot be determined, the subject will be excluded from the corresponding subgroup analysis. If the number of subjects in any subgroup is less than 10, that subgroup will not be presented.

Subpopulations will be defined by the following baseline characteristics.

- Age (<35, ≥35 to <65, ≥65 years).
- Gender.
- Race (Asian, Black or African American, White, Other).
- Duration of UC (<1 year, ≥1 to <3 years, ≥3 to <7 years, ≥7 years).
- Geographic region (Appendix C).
- Baseline disease activity (baseline complete Mayo score: Mild <6, Moderate=6 to8, Severe=9 to 12).
- Baseline fecal calprotectin (≤250 µg/g, >250 to ≤500 µg/g, >500 µg/g).
- Disease localization (proctosigmoiditis, left-sided colitis, extensive colitis, or pancolitis).
- Clinical remission status at Week 6.
- Prior TNF-α antagonist therapy (naïve, failure. Failure will be further categorized by type of failure – Inadequate response, Loss of response, Intolerance).
- Prior immunomodulator and TNF-α antagonist failure (Y/N)
- Prior corticosteroids failure (Y/N)
- Prior immunomodulator failure (Y/N)
- Concomitant therapies: corticosteroids and immunomodulators (Concomitant corticosteroids only, concomitant immunomodulators only, concomitant corticosteroids and immunomodulators, no concomitant corticosteroids or immunomodulators).
- Worst prior treatment failure (subjects with prior TNF-α antagonist failure, subjects with prior immunomodulator failure but not TNF-α antagonist failure, subjects with prior corticosteroid failure).

7.8.6 Sensitivity Analysis

Analyses using the PPS population may be provided as a sensitivity analysis for primary endpoint and all secondary endpoints.

The Complete Mayo score and Partial Mayo score for each patient will be calculated for post-Screening visit per FDA Draft Ulcerative Colitis guidance (August 2016). Refer to Section 7.1.2.2 for details. Primary efficacy endpoint and all secondary endpoints will be derived using this FDA-guided Mayo score calculation convention. Sensitivity analysis will be performed for primary efficacy endpoint, all secondary endpoints, and subgroup analysis by prior use of anti-TNFα antagonist.

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In addition, if any clinical site has detected or reported significant noncompliance with regulatory requirements during the course of study, additional sensitivity analysis will be conducted for the primary efficacy endpoint in the FAS excluding all subjects from that particular site.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Vedolizumab serum concentrations will be summarized by scheduled time points using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing.

7.10 Other Outcomes

7.10.1 Immunogenicity Endpoints

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[redacted]

7.10.2 Histological Endpoints

CCI

[redacted]

7.10.3 Resource Utilization and Patient-Reported Outcome Endpoints

CCI

[redacted]

7.11 Safety Analysis

All safety analyses will be performed using the SAF unless otherwise specified. Data will be summarized by treatment groups. No statistical inference will be made for safety analyses.

7.11.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Agencies (MedDRA).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts or worsens on or after Study Day 1 (defined as day first dosed), and no more than 18 weeks/126 days after the last dose of study drug. All TEAEs will be listed by subject number and MedDRA coding. A listing of all unique coded terms will also be provided.

The number and percentage of subjects with TEAEs will be summarized in several different tables, in addition, exposure adjusted AE rates will be summarized as well:

- An overview TEAE table in SAF-C.
- All TEAEs by system organ class (SOC), high level term (HLT), and preferred term (PT).
- Treatment-emergent adverse events of special interested (AESIs) (ie, serious infections including opportunistic infection such as PML, malignancies, liver injury, infusion reactions, injection site reactions and hypersensitivity).
- Treatment-related TEAEs by SOC, HLT, and PT.
- Serious TEAEs which occur on or after the first dose date and up to 18 weeks/126 days after the last dose date of the study drug in subjects who do not enroll in open-label extension study or up to the first dose of the open-label extension study in those who do.
- Most frequent TEAEs by HLT and PT (sorted by frequency of HLT occurring in ≥5% of subjects).
- Most frequent treatment-related TEAEs by HLT and PT (sorted by frequency of HLT occurring in ≥2% of subjects).
- Severity of all TEAEs by SOC and PT (mild, moderate, or severe).
- Severity of treatment-related TEAEs by SOC and PT (mild, moderate, or severe).
- Relationship to study drug for all TEAEs by SOC and PT (not related, related).
- Exposure-adjusted TEAEs and serious TEAEs by SOC, HLT, and PT
- Exposure-adjusted treatment-emergent infections and serious treatment-emergent infections by SOC, HLT, and PT
- Subject mapping of TEAEs by SOC, HLT, and PT

A subject with 2 or more TEAEs within the same level of the MedDRA term will be counted only once in that level using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

Additional summaries of TEAEs will be provided that only include TEAEs that occur in the Maintenance Phase between the Week 6 dose and 18 weeks/126 days after the last dose date of the study drug, or up to the first dose of the OLE study, whichever comes first.

Additionally, treatment-emergent SAEs, deaths, and TEAEs resulting in premature discontinuation from study drug will be listed and summarized by SOC, HLT, and PT. The most frequent treatment-emergent non-serious AEs will also be summarized by SOC, HLT, and PT.

A pretreatment event (PTE) will be defined as an AE that starts before Study Day 1. A list of pretreatment AEs by subject number and MedDRA coding will be presented separately. Pretreatment AEs will be summarized by SOC and PT using SAF.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory variables will be summarized by treatment groups using descriptive statistics for baseline, postbaseline, and change from baseline to postbaseline values in SAF. Additional summary tables may be provided in SAF-I.

Individual results for clinical hematology and chemistry laboratory tests that are within the predefined "markedly abnormal laboratory value (MAV) criteria" (Appendix A) will be summarized in tables. All clinical laboratory data will be presented in data listings.

Elevated hepatic parameters will be summarized.

Summaries and listings of laboratory data will be presented in Système International (SI) and conventional units. MAV tables and listings will be presented in the unit specified in the MAV criteria in Appendix A.

7.11.3 Vital Signs

Vital signs will be summarized by treatment using descriptive statistics for Baseline, postbaseline, and change from Baseline to postbaseline values.

Individual vital signs which meet predefined criteria for abnormal changes from Baseline of vital signs (Appendix B) will be summarized in tables. All vital sign data will be presented in data listings.

7.11.4 12-Lead ECGs

ECG results will be interpreted using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The shift in ECG interpretation from Baseline will be summarized by treatment group.

All ECG data will be presented in a data listing.

7.11.5 Other Observations Related to Safety

Physical examination results will be presented in a data listing and will not be summarized. PML checklist data will be presented in data listings.

Data from the LTFU survey will be summarized descriptively.

7.12 Interim Analysis

No interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

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8.0 REFERENCES

Ratitch, B.R., Lipkovich, I. and O'Kelly, M. (2013). Combining Analysis Results from Multiply Imputed Categorical Data. PharmaSUG Proceedings 2013 - Paper SP03. https://www.pharmasug.org/proceedings/2013/SP/PharmaSUG-2013-SP03.pdf.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
Hemoglobin	<0.8 × LLN,	>1.2 × ULN
Hematocrit	<0.8 × LLN,	>1.2 × ULN
RBC count	<0.8 × LLN,	>1.2 × ULN
WBC count	$<2.0 \times 10^3/\mu L$	>1.5 × ULN
Platelet count	$<70 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$

RBC=red blood cell, WBC=white blood cell. LLN=lower limit of normal, ULN=upper limit of normal.

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
ALT	--	>3x ULN
AST	--	>3x ULN
GGT	--	>3x ULN
Alkaline phosphatase	--	>3x ULN
Total bilirubin	--	>2.0 mg/dL
Albumin	<2.5 g/dL	--
Total protein	<0.8x LLN	>1.2x ULN
Creatinine	--	>2.0 mg/dL
Sodium	<130 mEq/L	>150 mEq/L
Potassium	<3.0 mEq/L	>6.0 mEq/L
Bicarbonate	<8.0 mmol/L	--
Chloride	<75 mmol/L	>126 mmol/L
Calcium	<1.50 mmol/L	>3.25 mmol/L
Glucose	≤2.8 mmol/L	≥20 mmol/L
Phosphorous	<0.52 mmol/L	>2.10 mmol/L
CPK	--	>5x ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, CPK=creatine phosphokinase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Criterion Value	Change Relative to Baseline
Pulse	≥120 beats/min	
	≤50 beats/min	
Systolic blood pressure	≥180 mm Hg	
	≤85 mm Hg	
Diastolic blood pressure	≥110 mm Hg	
	≤50 mm Hg	
Body temperature	<35.6 °C	
	>37.7 °C	

Appendix C 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** **1 = Mild disease** **2 = Moderate disease** **3 = Severe disease**	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 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 D Geographic Regions

Region	Countries		
North America	Canada	United States	
South America	Argentina	Brazil	Columbia
	Mexico		
Western/ Northern Europe	Belgium	Denmark	Germany
	Italy	Lithuania	Netherlands
	Spain	Sweden	United Kingdom
Central Europe	Czech Republic	Hungary	Poland
		Serbia	Slovak Republic
Eastern Europe	Bosnia and Herzegovina	Bulgaria	Croatia
	Estonia	Israel	Russia
	Turkey	Ukraine	
Asia / Africa / Australia	Australia	Japan	Republic of Korea
	South Africa		

Appendix E AEs of Special Interest

Events	MedDRA Terms or definitions
Malignancies	SOC: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)
Infections	SOC: INFECTIONS AND INFESTATIONS
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.
Injection site reaction	Injection Site Reaction (HLT)
Hypersensitivity Reactions	Anaphylactic/anaphylactoid shock conditions SMQ (broad). Angioedema SMQ (broad). Hypersensitivity SMQ (broad).
PML	Human polyomavirus infection PT JC virus infection PT Leukoencephalopathy PT Progressive multifocal leukoencephalopathy PT JC virus CSF test positive PT Polyomavirus test positive PT JC polyomavirus test positive PT
Liver injury	Cholestasis and jaundice of hepatic origin SMQ (Broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad) Hepatitis, non-infectious SMQ (Broad) Liver related investigations, signs and symptoms SMQ (Narrow) Liver infections SMQ (Broad)

Appendix F Prior Therapies

	Systemic Corticosteroids	Immunomodulators	TNFα Antagonists
CRF label	Systemic Corticosteroids	Azathioprine	Infliximab
	Budesonide	6-Merrcaptopurine	Adalimumab
		Methotrexate	Golimumab

Appendix G Patient Reported Outcomes

Table G1: Patient Reported outcomes – IBDQ, EQ-5D and WPAI-UC

Variable	Subscore	Calculation
IBDQ	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	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 component score	Ranging from 1 to 3
	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.	
WPAI-UC	Percentage of work time missed because of UC in the past seven days	Q2/(Q2+Q4)
	Percentage of impairment experienced while at work in the past seven days because of UC	Q5/10
	Overall work productivity loss	Q2/(Q2+Q4)+ [(1- Q2/(Q2+Q4))×Q5/10]
	Percentage of impairment in daily activities due to UC in the past 7 days	Q6/10

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	18-Jun-2018 18:15 UTC
	Clinical Approval	18-Jun-2018 19:22 UTC
	Biostatistics Approval	18-Jun-2018 19:27 UTC
	Pharmacovigilance Approval	19-Jun-2018 09:37 UTC