Statistical Analysis Plan

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Study Number: MLN0002SC-3030

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Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: MLN0002SC-3030

A Phase 3b Open-Label Study to Determine the Long-term Safety and Efficacy of Vedolizumab Subcutaneous in Subjects with Ulcerative Colitis and Crohn's Disease

Vedolizumab SC Long-Term Open-Label Extension Study

PHASE 3b

Version**:** Final 3.0

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Prepared by:

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1.1 APPROVAL SIGNATURES

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

2.0 TABLE OF CONTENTS

1.0 TITLE PAGE 1
1.1 APPROVAL SIGNATURES 2
2.0 TABLE OF CONTENTS 3
3.0 LIST OF ABBREVIATIONS 6
4.0 OBJECTIVES 8
4.1 Primary Objectives 8
4.2 Secondary Objectives 8
4.3 Exploratory Objectives 8
4.4 Study Design 8
5.0 ANALYSIS ENDPOINTS 11
5.1 Primary Endpoint 11
5.2 Secondary Endpoints 11
5.3 Resource Utilization and Patient Reported Outcome Endpoints 11
5.4 Exploratory Endpoints 12
6.0 DETERMINATION OF SAMPLE SIZE 13
7.0 METHODS OF ANALYSIS AND PRESENTATION 14
7.1 General Considerations 14
7.1.1 Study Terms and Definitions 14
7.1.2 Convention for Calculations of Partial Mayo Scores for UC Subjects 15
7.1.3 Convention for Calculations of HBI Scores for CD Subjects 16
7.1.4 Duplicate Records due to Patient Self-Entered Data and Site Entered Data into Hand-held Device 16
7.1.5 Convention for Missing Efficacy Data 17
7.1.6 Baseline Definition 18
7.1.7 Definition of Study Days and Analysis Visit Window for MLN0002SC-3030 18
7.2 Analysis Sets 20
7.2.1 Efficacy Population 20
7.2.2 Safety Population 21
7.2.3 [redacted] 21
7.3 Disposition of Subjects 21
7.4 Demographic and Baseline Characteristics 22
7.5 Medical History and Concurrent Medical Conditions 23
7.6 Medication History and Concomitant Medications and Procedures 23
7.7 Conventions for Missing Concomitant Medications Dates 24

7.8 Study Drug Exposure and Compliance 24
7.9 Efficacy Analysis 25
7.9.1 Primary Efficacy Endpoint 25
7.9.2 Secondary Efficacy Endpoint 25
7.9.3 Patient Reported Outcomes (PROs) Endpoints 27
7.10 [redacted] 27
7.11 Other Outcomes 28
7.11.1 [redacted] 28
7.12 Safety Analysis 28
7.12.1 Adverse Events (AE) 28
7.12.2 Conventions for Missing Adverse Events Dates 30
7.12.3 Clinical Laboratory Evaluations 31
7.12.4 Vital Signs 31
7.12.5 12-Lead ECGs 31
7.12.6 Other Observations Related to Safety 31
7.13 Interim Analysis 32
7.14 Changes in the Statistical Analysis Plan 32
7.14.1 Revision History 33
8.0 REFERENCES 34

LIST OF IN-TEXT TABLES

Table 7.a Analysis Visit Window Convention for MLN0002SC-3030 19

LIST OF IN-TEXT FIGURES

Figure 4.a Schematic of Study Design 10

LIST OF APPENDICES

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values 35
Appendix B Criteria for Markedly Abnormal Values for Vital Signs 36
Appendix C Mayo Score Calculation Worksheet 37
Appendix D HBI for the Assessment of Crohn's Disease Activity 39
Appendix E Geographic Regions 40
Appendix F AEs of Special Interest 41

Appendix G Prior Therapies....42
Appendix H Patient Reported Outcomes– IBDQ, EQ-5D and WPAI-UC 43

3.0 LIST OF ABBREVIATIONS

Term	Definition
5-ASA	5-aminosalicylate
AE	adverse event
AESI	adverse event of special interest
AI	autoinjector
[redacted]	[redacted]
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRF	Case Report form
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
EQ-5D	Euro Quality of Life-5D
ET	early termination
GI	Gastrointestinal(ly)
HBI	Harvey-Bradshaw Index
HLT	high level term
IBDQ	Inflammatory Bowel Disease Questionnaire
IA	interim analysis
ISAP	interim statistical analysis plan
IV	intravenous(ly)
LLN	lower limit of normal
LOCF	last observation carried forward
LTFU	long-term follow-up
MAV	markedly abnormal laboratory value
MedDRA	Medical Dictionary for Regulatory Activities
NSD	needle safety device
OLE	open-label extension
PFS	prefilled syringe
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PRO	patient-reported outcome
PT	preferred term
PTE	pretreatment event
QW	once every week
Q2W	once every 2 weeks
RAMP	Risk Assessment and Management Program for PML
SAE	serious adverse event

Term	Definition
SC	subcutaneous(ly)
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TRAE	treatment related AE
TNF-α	tumor necrosis factor- alpha
UC	ulcerative colitis
ULN	upper limit of normal
WPAI	Work Productivity and Activity Impairment

4.0 OBJECTIVES

4.1 Primary Objectives

To obtain data on long term safety and tolerability of vedolizumab subcutaneous (SC) in subjects with UC or CD.

4.2 Secondary Objectives

- To obtain data on adverse events of special interest ([AESIs]; serious infections including opportunistic infection such as progressive multifocal leukoencephalopathy [PML], liver injury, malignancies, injection site reactions or systemic reactions and hypersensitivity) in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on maintaining clinical response and clinical remission in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on patient-reported outcomes (PRO) in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on Work Productivity and Activity Impairment (WPAI-UC; WPAI-CD) in UC and CD subjects receiving long-term vedolizumab SC treatment.
- To obtain data on time to major UC- and CD-related events (hospitalizations, bowel surgeries, and procedures) in UC and CD subjects receiving long-term vedolizumab SC treatment.

4.3 Exploratory Objectives

[redacted]

4.4 Study Design

This is a phase 3b open-label extension (OLE) study to gather long-term safety and efficacy data of vedolizumab SC in subjects with UC and CD. All enrolled subjects will receive vedolizumab SC 108 mg. Establishing the long-term safety and tolerability of vedolizumab SC is a key component of the clinical development program of vedolizumab SC in UC and CD.

From this OLE study of vedolizumab SC therapy, data regarding the occurrence of important clinical events resulting from chronic vedolizumab SC administration will be obtained. Important clinical events including those related to safety and AESIs as well as efficacy (eg, maintenance of clinical remission/clinical response, quality of life, and various other health outcomes

measures) will be collected. Study MLN0002SC-3030 (hereafter SC-3030) will provide long-term safety data for vedolizumab SC dosing to complement the safety data gathered from Study MLN0002SC-3027 (hereafter SC-3027) in UC subjects and Study MLN0002SC-3031 (hereafter SC-3031) in CD subjects.

Subjects enrolling in this OLE study will have participated in the SC-3027 or SC-3031 study:

- Subjects with UC or CD who completed the Maintenance Phase (Week 52) will receive vedolizumab SC 108 mg Q2W.
- Subjects with UC or CD who withdrew early from the Maintenance Phase due to disease worsening or need for rescue medications from Week 14 will receive vedolizumab SC 108 mg once weekly (QW).
- Subjects with UC and CD who did not achieve a clinical response at Week 6 but who did achieve a clinical response at Week 14 after having received a third vedolizumab intravenous (IV) infusion at Week 6 will receive vedolizumab SC 108 mg Q2W.

Subjects who have UC/CD-related surgical interventions or study drug-related adverse events (AEs) leading to discontinuation from Study SC-3027 or SC-3031 will not be eligible to enroll into Study SC-3030.

At any time during Study SC-3030, subjects who experience treatment failure (ie, disease worsening, requirement for rescue medications):

While receiving vedolizumab 108 mg Q2W during this OLE study: will undergo dose escalation and continue to receive vedolizumab 108 mg QW

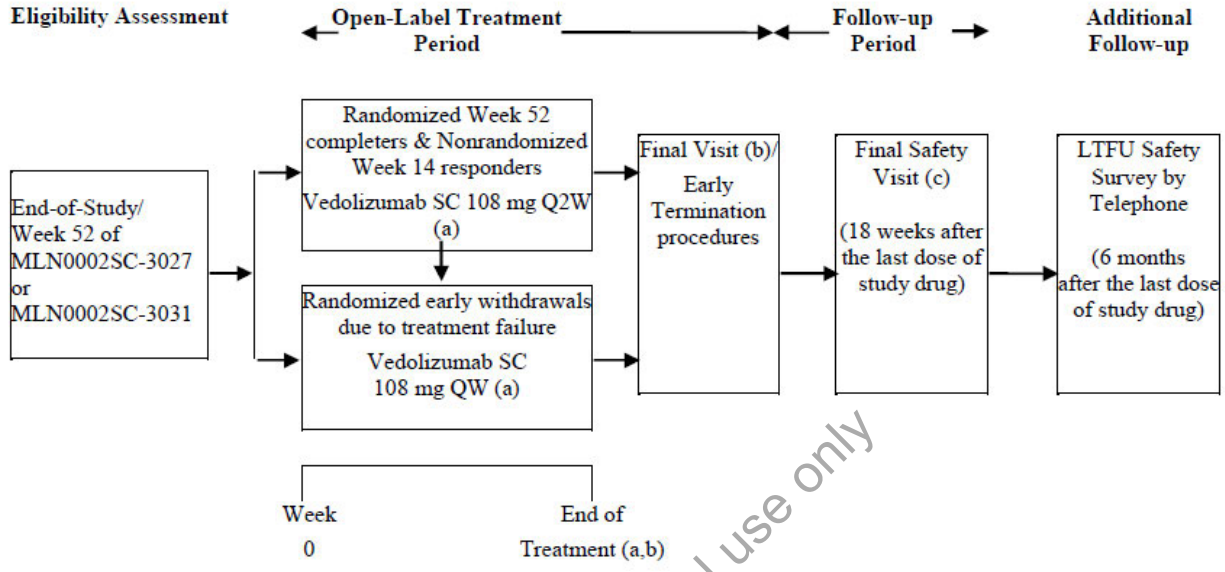
While receiving vedolizumab 108 mg QW during this OLE study: will be withdrawn from the study.

Subjects who have AEs related to study drug that lead to drug discontinuation or require a surgical intervention for their UC or CD during this OLE study will be withdrawn.

It is anticipated that the duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs, or if the subject withdraws from the study, or the sponsor decides to close the study. After the final dose of vedolizumab SC on the study (eg, due to withdrawal), subjects will complete a Final Safety Visit 18-weeks after the last dose received. Additionally, upon completion (or withdrawal) of this study, subjects will participate in a 6-month (from their last study drug dose) follow-up survey, at which time a questionnaire will be administered.

A schematic of the study design is included as Figure 4.a.

Figure 4.a Schematic of Study Design



LTFU=long-term follow-up.
(a) Subjects will switch to self-injection of vedolizumab SC in PFS+AI. Once the subject has switched to administer vedolizumab SC via PFS+AI, they will continue with all study related procedures using the chosen presentation until the completion of the study or requested otherwise by the sponsor. Subjects may be switched back to PFS or to PFS+NSD only at the sponsor's request if any concern or issue is identified with PFS+AI.
Japan only: Subjects will have the option to switch to self-injection of vedolizumab SC in PFS+NSD or PFS+AI at any scheduled or unscheduled visit beginning at the Week 16 visit.
(b) Duration of vedolizumab SC treatment will vary by subject based on continued benefit, but will be until vedolizumab SC is available in the subject's country commercially or through other access programs, or if the subject withdraws from the study, or the sponsor decides to close the study.
(c) Subjects who withdraw early will return 18 weeks after the last dose of vedolizumab SC for final safety assessments at the early termination (ET) Visit.

5.0 ANALYSIS ENDPOINTS

This study will provide long-term safety data for vedolizumab SC dosing to complement the safety data gathered from Study SC-3027 in UC subjects and Study SC-3031 in CD subjects. Secondary and exploratory [redacted] outcomes such as clinical remission, clinical response, and [redacted] will be assessed in subgroup of subjects to whom these endpoints are relevant.

5.1 Primary Endpoint

- Subject-year-adjusted treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) during long-term vedolizumab SC treatment.

5.2 Secondary Endpoints

- Subject-year-adjusted AESIs (including serious infections, including opportunistic infection such as PML, liver injury, malignancies, injection-site reactions or systemic reactions and hypersensitivity) during long-term vedolizumab SC treatment.
- Proportion of subjects with clinical response during long-term vedolizumab SC treatment using partial Mayo scores (defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding score of ≥1 or absolute rectal bleeding subscore of ≤1) in UC subjects and Harvey-Bradshaw Index (HBI) scores (defined as a ≥3-point decrease in HBI score from Baseline) in CD subjects (randomized early terminator CD subjects only [defined as randomized CD subjects withdrawn from the parent study between Week 6 and Week 52]).
- Proportion of subjects with clinical remission during long-term vedolizumab SC treatment using partial Mayo scores (defined as a partial Mayo score of ≤2 and no individual subscore >1 point) in UC subjects and HBI scores (defined as a HBI score of ≤4 points) in CD subjects.

5.3 Resource Utilization and Patient Reported Outcome Endpoints

- Changes from Baseline (Week 0) in Inflammatory Bowel Disease Questionnaire (IBDQ) total and subscale scores and EuroQoL (EQ-5D) utility and EQ-5D VAS scores in UC and CD subjects receiving long-term vedolizumab SC treatment.
- Changes from Baseline (Week 0) in work productivity and activity impairment scores (WPAI-UC; WPAI-CD) in UC and CD subjects receiving long-term vedolizumab SC treatment.
- Time to major UC and CD-related events (hospitalizations, bowel surgeries, and procedures) in UC and CD subjects receiving long-term vedolizumab SC treatment.

5.4 Exploratory Endpoints

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The total sample size is estimated to be approximately 692 subjects:169 UC and 348 CD subjects who will have been randomized into the Maintenance Phase of Study SC-3027 or SC-3031; and approximately 73 UC and 102 CD subjects who will have achieved a clinical response at Week 14 after the third vedolizumab IV infusion after not having achieved a clinical response at Week 6 will enter this study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

The calculation of statistics 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 with non-missing values, 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

Pertaining to UC Subjects

Term	Definition
Clinical remission	A partial Mayo score of ≤2 and no individual subscore >1 point
Clinical response	A reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding score of ≥1 or absolute rectal bleeding subscore of ≤1
Disease Worsening	– While participating in study SC-3027: An increase in partial Mayo score of ≥3 points on 2 consecutive visits from the Week 6 (of SC-3027 study) value (or an increase to 9 points on 2 consecutive visits if the Week 6 value >6) and a minimum partial Mayo score of ≥5. – While participating in study SC-3030: An increase in partial Mayo score ≥3 points on 2 consecutive visits from the Week 0 (of SC-3030 study) value (or an increase to 9 points on 2 consecutive visits if the Week 0 value >6) and a minimum partial Mayo score of ≥5.
Requirement for rescue medication	– While participating in study SC-3027 at Week 14 and beyond: the receipt of, or need for, any rescue medications or an increase in dose of a baseline medication required for new or unresolved UC symptoms (other than antidiarrheals for control of chronic diarrhea). – While participating in study SC-3030: Any new medication to treat a new or unresolved luminal manifestation of UC, with the following exceptions: oral and topical 5-aminosalicylate (5-ASA) treatment, oral corticosteroids per the guidelines outlined in the Oral Corticosteroid Dosing and Tapering Regimen Section of the protocol, oral corticosteroid, azathioprine or 6-MP, antibiotics, antidiarrheals for control of chronic diarrhea, probiotics (eg, Culturelle, *Saccharomyces boulardii*).
Treatment Failure	Defined as disease worsening, need for rescue medications, or need for surgical interventions for treatment of UC.

Pertaining to CD Subjects

Term	Definition
Clinical remission	- While participating in study SC-3031, clinical remission is defined as a Crohn's Disease Activity Index (CDAI) score ≤150. - While participating in study SC-3030, clinical remission is defined as a Harvey-Bradshaw Index (HBI) score of ≤4 points.
Clinical response	- While participating in study SC-3031, clinical response is defined as a ≥70 point decrease in CDAI score from Baseline (Week 0 of SC-3031 study). Enhanced clinical response is defined as a ≥100 point decrease in CDAI score from Baseline (Week 0 of SC-3031 study). - While participating in study SC-3030, clinical response is defined as a ≥3-point decrease in HBI score from Baseline (Week 0 of SC-3030 study).
Disease Worsening	– While participating in study SC-3031: A ≥100-point increase in CDAI score on 2 consecutive visits from the Week 6 (of SC-3031 study) value at any study visit and a minimum CDAI score of 220 points. – While participating in study SC-3030: A ≥4-point increase in HBI score on 2 consecutive visits from the Week 0 (of SC-3030 study) value and a minimum HBI score of 7 points.
Requirement for rescue medication	– While participating in study SC-3031 at Week 14 and beyond: the receipt of, or need for, any rescue medications or an increase in dose of a baseline medication required for new or unresolved CD symptoms (other than antidiarrheals for control of chronic diarrhea). – While participating in study SC-3030: Any new medication to treat a new or unresolved luminal manifestation of CD, with the following exceptions: oral and topical (rectal) 5-ASA treatment, oral corticosteroids per the guidelines outlined in the Oral Corticosteroid Dosing and Tapering Regimen Section of the protocol, oral corticosteroid, methotrexate, antibiotics, antidiarrheals for control of chronic diarrhea, probiotics (eg, Culturelle, *Saccharomyces boulardii*).
Treatment Failure	Defined as disease worsening, need for rescue medications, or need for surgical interventions for treatment of CD.

7.1.2 Convention for Calculations of Partial Mayo Scores for UC Subjects

7.1.2.1 Gemini Approach

UC disease activity will be followed throughout this OLE study using the partial Mayo score, a standardized measure for UC trials that includes 3 of the 4 components of the complete Mayo score. 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.

7.1.2.2 FDA Guidance Approach

As a sensitivity analysis, the partial Mayo score for each patient will be calculated for eligibility assessment visit per FDA Draft Ulcerative Colitis guidance (August 2016). 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.

This approach only applies to the secondary efficacy endpoints of clinical response and clinical remission by visit.

7.1.3 Convention for Calculations of HBI Scores for CD Subjects

CD disease activity will be followed throughout this OLE study using the HBI (Appendix D), a standardized measure for CD trials that has previously been demonstrated to correlate highly with CDAI.

HBI consists of 5 clinical parameters, which are general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications. Each variable is scored individually, with higher scores indicating greater disease activity. The HBI score is defined as the total of the 5 subscores.

7.1.4 Duplicate Records due to Patient Self-Entered Data and Site Entered Data into Hand-held Device

SC dosing done during on-site visits will be recorded in the electronic case report form (eCRF). If patients accidentally record SC dosing done during on-site visits on the same day of clinic visit in the eDiary, data recorded in the eCRF will be used.

If UC 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.

If CD patients have multiple entries on the same day for patient reported items into the hand-held device, the worst results will be used for HBI score calculation.

7.1.5 Convention for Missing Efficacy Data

Unless otherwise stated, the missing data for efficacy endpoints will be handled as follows:

Missing data for dichotomous (i.e., proportion-based) endpoints in SC-3030:
In general, missing data prior to study completion of premature study discontinuation will be imputed using the non-responder imputation method. Other missing data options may be explored.

- For subjects who have completed or withdrawn from SC-3030 by the time of interim data cut or at final analysis, the missing data for determination of the status of dichotomous efficacy endpoints will be imputed using the non-responder imputation method.
- [Interim analysis only] For ongoing subjects, missing data for determination of the status of dichotomous efficacy endpoints at the visits that have been reached by the time of interim data cut will be imputed using the non-responder method. Data for future visits that have not been reached by the time of the interim data cut will not be imputed.
- [Optional handling for sensitivity analysis at final analysis stage]
  If deemed appropriate, alternative handling of missing data can be considered:
  a) For subjects who have discontinued prematurely from SC-3030, missing data for determination of the status of dichotomous efficacy endpoints at time points after their premature discontinuation will be imputed using the non-responder imputation method (as described above). For subjects who have completed study SC-3030 or completed the study early and transitioned to the commercial drug, missing data for determination of their status of dichotomous efficacy endpoints will not be imputed for time points after their time of study treatment completion (EOT). Instead, those subjects will be excluded from the analyses of such endpoints for the time points after their study treatment completion (observed data up to EOT+28 days will be included in the analysis).
  b) For subjects who have completed or withdrawn from SC-3030, the missing data for determination of the status of dichotomous efficacy endpoints after completion or withdrawal will not be imputed, and subjects will not be counted in the denominator for those time points (observed-data analysis).

Missing data for continuous endpoints prior to study completion of premature study discontinuation will be imputed using the 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 the baseline observation carried forward method. Other missing data imputation methods may be explored.

- For subjects who have completed or withdrawn from SC-3030 by the time of interim data cut or at final analysis, the missing data for continuous efficacy endpoints will be imputed using LOCF.
- [Interim analysis only] For ongoing subjects, missing data for continuous efficacy endpoints at the visits that have been reached by the time of interim data cut will be imputed using LOCF. Data for future visits that have not been reached by the time of the interim data cut will not be imputed.
- [Optional handling for sensitivity analysis at final analysis stage]
  If deemed appropriate, alternative handling of missing data can be considered:
  a) For subjects who have discontinued prematurely from SC-3030, missing data for continuous efficacy endpoints at time points after their premature discontinuation will be imputed using LOCF.
  For subjects who have completed study SC-3030 or completed the study early and transitioned to the commercial drug, missing data for continuous efficacy endpoints will not be imputed for time points after their time of study treatment completion (EOT). Instead, those subjects will be excluded from the analyses of such endpoints for time points after their study treatment completion (observed data up to EOT+28 days will be included in the analysis).
  b) For subjects who have completed or withdrawn from SC-3030, the missing data for continuous efficacy endpoints will not be imputed, and missing data will not be included in the analysis for those time points (observed-data analysis).

7.1.6 Baseline Definition

Unless otherwise stated, the baseline is defined as the last non-missing measurement prior to or on the date of the first dose of the study drug (Study Day 1). In particular, two baseline definitions will be used in the analysis:

- SC-3030 Week 0 baseline is defined as the last non-missing measurement prior to or on the date of the first dose of the study drug in SC-3030.
- SC-3027/SC-3031 baseline is defined as the last non-missing measurement prior to or on the date of the first dose of the study drug of SC-3027/SC-3031.

7.1.7 Definition of Study Days and Analysis Visit Window for MLN0002SC-3030

In study SC-3030, treatment begins on the date of the first dose of study drug in the extension study as recorded in the eCRF.

In protocol Amendment 10, the frequency of clinic visits after at least Week 72 to every 24 weeks, starting at the next visit that is a multiple of 24 (eg, Week 96, 120, 144, etc), while requiring subjects to return to the site every 8 weeks between these clinic visits to receive an 8-week supply of study medication for at-home administration. Analysis windows will not be updated since there is a good number of subjects who completed visits beyond Week 72 before protocol amendment 10 was implemented in their sites.

Study day for SC-3030 will be calculated relative to the date of the first dose of study drug in the extension 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.

The visit windows for the post baseline visits (QW and Q2W dosing) are defined in Table 7.a Given that QW and Q2W subjects have different clinical visits per study protocol, Weeks 1, 2, and 4 analysis visits are defined separately for QW and Q2W subjects.

If a subject has more than 1 measurement in the same visit window, the measurement closest to the target day will be used. If 2 measurements in the same window are of equal distance to the target day, the measurement that occurs after the target day will be used. If 2 or more measurements occur on the same day, the last value obtained will be used if the time of measurements are reported; otherwise, the average value will be used, unless stated otherwise.

Table 7.a Analysis Visit Window Convention for MLN0002SC-3030

Analysis Visit	Target Day	Vital Signs/Chemistry/Hematology/ Partial Mayo-UC/HBI-CD	IBDQ/ EQ-5D/ WPAI-UC/WPAI-CD/ [redacted]
3030 Baseline (Week 0)	Day 1	≤1	≤1
Week 1 (QW)[a]	Day 7	2-18	-
Week 2 (Q2W)[a]	Day 14	2-21	-
Week 4[b]	Day 28	19-42 for QW 22-42 for Q2W	-
Week 8	Day 56	43-84	-
Week 16	Day 112	85-140	-
Week 24	Day 168	141-196	2-252
Week 32	Day 224	197-252	-
Week 40	Day 280	253-308	-
Week 48	Day 336	309-364	253-420
Week 56	Day 392	365-420	-
Week 64	Day 448	421-476	-
Week 72	Day 504	477-532	421- 588
Week 80	Day 560	533-588	-
Week 88	Day 616	589-644	-
Week 96	Day 672	645-700	589-756
Week 104	Day 728	701-756	-
Week 112	Day 784	757-812	-
Week 120	Day 840	813-868	757-924
Week 128	Day 896	869-924	-
Week 136	Day 952	925-980	-
Week 144	Day 1008	981-1036	925- 1092
Week 152	Day 1064	1037-1092	-

Analysis Visit	Target Day	Vital Signs/Chemistry/Hematology/ Partial Mayo-UC/HBI-CD	IBDQ/ EQ-5D/ WPAI-UC/WPAI-CD/ [redacted]
Week 160	Day 1120	1093-1148	-
Week 168	Day 1176	1149-1204	1093- 1260
Week 176	Day 1232	1205-1260	-
Week 184	Day 1288	1261-1316	-
Week 192	Day 1344	1317-1372	1261- 1428
Week 200	Day 1400	1373-1428	-
Week 208	Day 1456	1429-1484	-
Week 216	Day 1512	1485-1540	1429- 1596
Week 224	Day 1568	1541-1596	-
Week 232	Day 1624	1597-1652	-
Week 240	Day 1680	1653-1708	1597-1764
Week 248[c]	Day 1736	1709-1764	-
Week 256	Day 1792	1765-1820	-
Week 264	Day 1848	1621-1876	1765-1932
Week 272	Day 1904	1877-1932	-
Week 280	Day 1960	1933-1988	-
Week 288	Day 2016	1989-2044	1933-2100
Week 296	Day 2072	2045-2100	-
Week 304	Day 2128	2101-2156	-
Week 312	Day 2184	2157-2212	2101-2268
Week 320	Day 2240	2213-2268	-
Week 328	Day 2296	2269-2324	-
Week 336	Day 2352	2325-2380	2269-2436
Week 344[c]	Day 2408	2381-2436	-

[a] Week 1 for QW subjects only, and week 2 for Q2W subjects only.
[b] Visit windows for week 4 are defined separately for QW and Q2W subjects.
[c] Actual last visit may vary depending on the data cut.

7.2 Analysis Sets

7.2.1 Efficacy Population

The efficacy population is defined as the Full Analysis Set (FAS) including all enrolled UC subjects (FAS-UC) and all enrolled CD subjects (FAS-CD) of SC-3030. Analysis of efficacy variables will be conducted in the FAS. Unless otherwise stated, the efficacy data of SC-3030 will be summarized by previous treatment groups in the parent study and by scenarios defined as follows:

Scenario 1 (randomized early terminator subjects): includes the randomized subjects withdrawn from parent study between week 6 and week 52 and are eligible to enroll in SC-3030 (use SC-3030 Week 0 baseline for comparison);

Scenario 2 (randomized completer subjects): include the randomized subjects who have completed week 52 of the parent study (either vedolizumab or placebo, use parent study baseline for comparison);

Scenario 3 (nonrandomized Week 14 responder subjects): include the subjects who were nonrandomized Week 14 responders of parent study (use parent study baseline for comparison).

7.2.2 Safety Population

The safety population is defined as the Safety Analysis Set (SAF) including all subjects who receive at least 1 dose of study medication during Study SC-3030. Analysis of safety data will be conducted in the SAF. Unless otherwise stated, the safety data of SC-3030 will be summarized by previous treatment groups in the parent study for UC (SAF-UC) and CD (SAF-CD) subjects separately.

7.2.3 [redacted]

[redacted]

7.3 Disposition of Subjects

A subject disposition summary will be provided in FAS-UC and FAS-CD separately. Subjects' study completion data, including reasons for premature termination, will be provided in listings and also summarized. Number of subjects enrolled by site will be summarized. Significant protocol deviations (SPD) captured on the electronic CRF will also be summarized.

Summary of analysis sets will be presented by UC and CD subjects separately among all enrolled subjects.

To assess the impact of COVID-19 on the safety of participating subjects, the following analyses of COVID-19 impact will be conducted if data permits. Additional tables and listings may be generated.

Disposition of subjects based on the COVID-19 related discontinuation, including discontinuation due to adverse events in light of COVID-19 infection and discontinuation due to COVID-related reasons other than COVID-infection (eg, travel limitation, reduced site staff, etc) using Full Analysis Set

Significant protocol deviations due to COVID-19 pandemic will be summarized descriptively using Full Analysis Set

Summary of COVID-19 Impact including the summary statistics of Number of Missed Visits, Visits with Missed Assessments and Visits with Alternative method of Contact and the number and percentage of subjects with at least one missed visit and missed visits by study visit.

7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics variables will be summarized for FAS-UC and FAS-CD, separately. For FAS-UC, the data will be summarized by previous treatment groups in parent study SC-3027 (nonrandomized week 14 responders, placebo, Vedolizumab SC, Vedolizumab IV). For FAS-CD, the data will be summarized by previous treatment groups in parent study SC-3031 (nonrandomized week 14 responders, placebo, Vedolizumab SC).

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

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

Duration of UC (<1 year, ≥1 to <3 years, ≥3 to <7 years, ≥7 years).

Subjects without prior corticosteroids or immunomodulators.

Subjects with only prior corticosteroids.

Subjects with only prior immunomodulators.

Subjects with prior corticosteroids and immunomodulators.

Subjects without concomitant corticosteroids or immunomodulators use at baseline (SC-3027).

Subjects with only concomitant corticosteroids use at baseline (SC-3027).

Subjects with only concomitant immunomodulators use at baseline (SC-3027).

Subjects with concomitant corticosteroids and immunomodulators use at baseline (SC-3027).

Prior tumor necrosis factor-alpha (TNF-α) antagonist use (Naïve, failure).

Subjects with prior immunomodulator and prior TNF-α antagonist failure.

Worst prior treatment failure (subjects with prior TNF-α antagonist failure, subjects with prior immunomodulator failure, subjects with prior corticosteroid failure).

SC-3027 Baseline disease activity (baseline complete Mayo score: Mild <6, Moderate = 6 to 8, severe = 9 to 12)

SC-3030 Week 0 disease activity (Week 0 partial Mayo score: Moderate <6, severe ≥6).

[redacted]

Disease localization (Proctosigmoiditis, Left sided colitis, Extensive colitis, Pancolitis).

Extraintestinal Manifestations.

The following CD-related baseline characteristics will be summarized for the FAS-CD:

Duration of CD (<1 year, ≥1 to <3 years, ≥3 to <7 years, ≥7 years).

Subjects without prior corticosteroids or immunomodulators.

Subjects with only prior corticosteroids.

Subjects with only prior immunomodulators.

Subjects with prior corticosteroids and immunomodulators.

Subjects without concomitant corticosteroids or immunomodulators use at baseline (SC-3031).

Subjects with only concomitant corticosteroids use at baseline (SC-3031).

Subjects with only concomitant immunomodulators use at baseline (SC-3031).

Subjects with concomitant corticosteroids and immunomodulators use at baseline (SC-3031).

Prior TNF-α antagonist use (Naïve, exposed but not failure, failure).

Subjects with prior immunomodulator and prior TNFα antagonist failure.

Worst prior treatment failure (subjects with prior TNFα anatomist failure, subjects with prior immunomodulator failure, subjects with prior corticosteroid failure).

SC-3031 Baseline and SC-3030 Week 0 disease activity (CDAI: Moderate ≤330, severe >330).

[redacted]

History of prior surgery for CD.

Disease localization (Ileum only, Colon only, Ilocolonic, other).

History of fistulizing Disease.

Fistula status at Baseline (draining, all closed, none).

Extraintestinal manifestations.

Demographic and disease-related characteristics data are as collected at the start of parent study unless specified otherwise.

7.5 Medical History and Concurrent Medical Conditions

Medical history (obtained from parent study) and concurrent medical conditions will be presented in a data listing and will be summarized in SAF-UC and SAF-CD.

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 126 days after the last dose of the study drug.

The number and percentage of subjects taking each concomitant medication during the OLE study will be summarized for the SAF-UC and SAF-CD separately. 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:

Concomitant medications that started and stopped prior to Baseline (SC-3030 Week 0).

Concomitant medications that started prior to and were ongoing at Baseline (SC-3030 Week 0).

Concomitant medications that started after Baseline (SC-3030 Week 0).

Concomitant medications that were ongoing at Baseline (SC-3030 Week 0) and those that started after Baseline (SC-3030 Week 0).

Data listings of Concomitant medications of COVID-19 Vaccine will be presented separately from other Concomitant mediations

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

7.7 Conventions for Missing Concomitant Medications Dates

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

If the start date is missing or partial:

- If the day is missing, the start day will be the first day of the month
- If the month is missing, the start month will be the month corresponding to 90 days prior to the first study medication date
- If the year is missing, the start year will be the minimum of the year of the first clinic visit or the year of the informal consent date
- If the entire date is missing, the start date will be the date of first study drug administration

If the stop date is missing, partial or “continuing:”

- If the day is missing, the stop day will be the last day of the month reported
- If the month is missing, the stop month will be 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 will be the year in which the last assessment occurred

7.8 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized in SAF-UC and SAF-CD.

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. Descriptive statistics for the total number of days on study drug will be generated. In addition, total number of Vedolizumab SC injections will be summarized based on the SAF.

Overall study drug compliance (%) will be determined as (total count of complete injections taken / total number of injections expected during study treatment) × 100%.

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 overall compliance ≥100% will be set to 100% in the analysis.

In addition, diary compliance will be determined as the percentage of days/visits during treatment with a diary entry and will be summarized based on FAS:

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

If data permits, additional data listing and/or summary table may be presented to evaluate the subject's adherence to study treatment as affected by COVID-19 pandemic, and subject's treatment accessibility as affected by COVID-19 pandemic.

7.9 Efficacy Analysis

Efficacy data for UC and CD subjects will be descriptively summarized in FAS-UC and FAS-CD, separately. No formal statistical testing will be performed.

7.9.1 Primary Efficacy Endpoint

Not applicable.

7.9.2 Secondary Efficacy Endpoint

Descriptive statistics, including 95% CIs, will be provided for all clinical efficacy variables of interest. Missing data will be handled as described in Section 7.1.5.

7.9.2.1 Efficacy Analysis for UC Subjects of MLN0002SC-3030

The following efficacy endpoints will be summarized by study visits in FAS-UC under the three scenarios (refer to Section 7.2.1), separately:

Proportion of subjects with clinical response during long-term vedolizumab SC treatment using partial Mayo scores in UC subjects;

Proportion of subjects with clinical remission during long-term vedolizumab SC treatment using partial Mayo scores in UC subjects.

Count, percentage and associated 95% CI using the Clopper-Pearson method will be provided for each treatment group under each scenario.

In addition, efficacy data will be analyzed in two different ways for the FAS-UC subjects in scenario 2 and scenario 3 as follows:

All subjects who have dose escalation from Q2W to QW will be regarded as non-responders or non-remitters (ie, failed Q2W treatment);

Dose escalation will not be taken into consideration for the determination of endpoint status.

Sensitivity analysis will be performed by calculating the partial Mayo score for each subject per FDA Draft Ulcerative Colitis guidance (August 2016) (refer to Section 7.1.2.2). Clinical remission and clinical response based on partial Mayo score will be derived accordingly.

7.9.2.2 Efficacy Analysis for CD Subjects of MLN0002SC-3030

The following efficacy variables will be summarized by study visits in the FAS-CD:

Proportion of subjects with clinical response during long-term vedolizumab SC treatment using HBI scores in CD subjects will be summarized for FAS-CD subjects in Scenario 1 only. This endpoint will not be summarized in Scenario 2 and Scenario 3 due to data collection limitation. CD disease activity are measured using two different indices in SC-3031 and SC-3030, CDAI and HBI respectively. For Scenario 2 and Scenario 3, baseline in parent study SC-3031 are used for comparison which is not available.

Proportion of subjects with clinical remission during long-term vedolizumab SC treatment using HBI scores in CD subjects will be summarized in the FAS-CD by scenarios.

Count, percentage and associated 95% CI using the Clopper-Pearson method will be provided.

In addition, proportion of subjects with clinical remission will be analyzed in two different ways for the FAS-CD subjects in scenario 2 and scenario 3 as follows:

All subjects who have dose escalation from Q2W to QW will be regarded as non-remitters (ie, failed Q2W treatment);

Dose escalation will not be taken into consideration for the determination of endpoint status.

Convention for Missing Week 0 HBI Data

Due to data collection limitations, some CD subjects did not have HBI data collected at Week 0 of Study SC-3030, or whose HBI Week 0 data was collected after the date of the first treatment dose. Assuming that HBI data collected within 2 weeks after Day 1 (Week 0) are still representative for Week 0, for those subjects the missing Week 0 HBI data will be imputed using their Week 1 HBI data (QW subjects) or Week 2 HBI data (Q2W subjects), if available. Sensitivity analysis will be conducted by excluding subjects with missing HBI Week 0 assessments.

7.9.3 Patient Reported Outcomes (PROs) Endpoints

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

Changes from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total and subscale scores and Euro Quality of Life-5D (EQ-5D) utility and visual analog scale (VAS) scores.

Changes from Baseline in WPAI-UC and WPAI-CD scores.

Time to major IBD-related events (hospitalizations, surgeries, or procedures).

Patient-reported outcomes will be analyzed using FAS-UC and FAS-CD separately. PRO endpoints will be analyzed under three different scenarios (refer to Section 7.2.1), separately.

PRO endpoints are assessed at Week 24 and once every 24 weeks. Summary tables for PROs include baseline and measurements at each scheduled post-baseline assessment visit as observed and as imputed by LOCF. Changes from baseline at each scheduled visit and associated 95% two-sided CI will be presented.

Resources Utilization Outcomes collected in this study are as follows and are analyzed using FAS-UC and FAS-CD:

Proportion of subjects with UC-related hospitalization without any UC procedures (including colectomy), colectomies, and other UC-related procedures (for UC subjects);

Time to UC-related hospitalization, colectomies, or UC-related procedures (for UC subjects);

Proportion of subjects with CD-related hospitalization, bowel surgeries, or CD-related procedures (for CD subjects);

Time to CD-related hospitalization, bowel surgeries, or CD-related procedures (for CD subjects).

Resource utilization outcomes are analyzed using FAS-UC and FAS-CD. For time-to-event analyses, Kaplan-Meier method with 95% CI is used for summarizing UC- or CD-related events (hospitalizations, surgeries, and procedures).

7.10 [redacted]

[redacted]

7.11 Other Outcomes

7.11.1 [redacted]

[redacted]

7.12 Safety Analysis

All safety analysis will be performed using SAF, for UC and CD separately unless specified otherwise. Descriptive statistics will be calculated. No statistical testing will be performed.

Safety analysis will be conducted by previous treatment groups in parent study (including nonrandomized Week-14 responders, placebo, Vedolizumab SC, Vedolizumab IV for SC-3027, and nonrandomized Week-14 responders, placebo, Vedolizumab SC for SC-3031).

Summaries of safety data such as Laboratory, vital sign, and ECG are provided for data collected on subjects during study SC-3030 up to the final safety visit.

7.12.1 Adverse Events (AE)

All AEs will be coded using the Version 21.0 or higher of Medical Dictionary for Regulatory Agencies (MedDRA). In this dictionary, each verbatim term is coded to a lower level term, and then mapped to a preferred MedDRA term, which is then mapped to a system organ class (SOC).

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. The number and percentage of subjects with TEAEs will be summarized. A listing of all unique coded terms will also be provided.

Summary of TEAEs, Serious TEAEs, and AESIs will be presented based on the SAF. The number and percentage of subjects with TEAEs will be summarized in several different tables, in addition, exposure-adjusted AE rates will also be summarized:

Overview of TEAEs.

All TEAEs by SOC, high level term (HLT), and preferred term (PT).

AESIs (ie, serious infections including opportunistic infection such as PML, malignancies, liver injury, injection site reactions and hypersensitivity; Appendix F) by SOC, HLT, and PT.

Treatment-related TEAEs by SOC, HLT, and PT.

Serious TEAEs by SOC, HLT, and PT (subject and event level).

Most frequent TEAEs by SOC, HLT and PT (sorted by frequency of PT occurring in ≥5% of subjects).

Most frequent Treatment-related TEAEs by SOC, HLT and PT (sorted by frequency of PT 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 SAEs by SOC, HLT, and PT.

Exposure-adjusted infections and serious infections 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).

Additionally, TEAEs resulting in death, 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 (subject and event level).

Tables of TEAEs, serious TEAEs, AESIs will be generated in overall UC subjects, overall CD subjects, and UC and CD combined population. Tables of TEAEs, serious TEAEs, AESIs will also be generated for subjects with Q2W dose, subjects with QW dose, and subjects who have dose escalation from Q2W to QW during Study SC-3030.

Subgroup Analysis

In addition to overall safety summary, subgroup analysis will be performed in UC and CD subjects separately for the summary of TEAEs, serious TEAEs, exposure-adjusted serious TEAEs, and exposure-adjusted infections and serious infections:

By age group (<65, ≥65 years).

By race group (White, Black, Asian, and Other).

By gender group (Male, Female).

By SC-3030 Week 0 baseline disease activity (moderate [UC: Baseline Partial Mayo Score <6, CD: CDAI ≤330], severe [UC: Baseline Partial Mayo Score ≥6, CD: CDAI >330]).

By body weight categories (<70 kg, 70 to 90 kg, >90 kg).

By prior TNF-α antagonist therapy.

7.12.2 Conventions for Missing Adverse Events Dates

Every effort will be 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 will be imputed according to the following conventions:

1) If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
    - First study medication date
    - Consent date (for SAEs only)
2) If an onset date is incomplete, the derived onset date will be calculated following:
    - Missing day, but month and year present: the day will be imputed as the 15th of the month. If the month and year are equal to the month and year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
    - Missing day and month, but year present: the day and month will be imputed as the 15th June of the year. If the year is equal to the year of the first study medication dose and the first study medication dose occurs after the imputed date, the derived onset date will be set equal to the first study medication date. If the AE end date occurs prior to the imputed date, the derived onset date will be set equal to the AE end date.
    - If the imputed AE onset date occurs after the database lock date, the imputed AE onset date will be imputed as the database lock date.

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

1) If an end date is missing, the derived end date will be imputed as the last assessment date, assuming that the last assessment occurs after the AE start. If the last assessment occurs prior to the AE start date, the derived end date will be imputed as the AE start date.
2) If an end date is incomplete, the derived end date will be calculated following:

- Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month.
- Missing day and month, but year present: the day and month will be 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 will be imputed as the database lock date.

7.12.3 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.

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. 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 System International (SI) and conventional units. MAV tables and listings will be presented in the unit specified in the MAV criteria in Appendix A.

7.12.4 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 will be summarized in tables. All vital sign data will be presented in data listings. MAV criteria for vital signs are listed in Appendix B.

7.12.5 12-Lead ECGs

The SC-3030 Week 0 baseline ECG value will be carried from Week 52/ET visit of the parent study (SC-3027 or SC-3031), or the relevant visit for nonrandomized Week 14 responders. All 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 UC and CD separately.

All ECG data will be presented in a data listing.

7.12.6 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.

7.13 Interim Analysis

An interim analysis was conducted to support the BLA/MAA filing for Vedolizumab SC in UC. Details of the planned analyses and data presentations for the first interim were described in the Interim Statistical Analysis Plan dated 13 July 2018.

A second interim analysis will be conducted to support the sBLA/MAA filing for Vedolizumab SC in CD, which is within the framework of this SAP. All available safety and efficacy data in Study SC-3030 by the time of interim data cut will be included in the second interim analysis with the following exceptions:

1. Efficacy and PRO data for UC patients in Study SC-3030 will not be included.

[redacted]

[redacted]

Additional interim analyses and reports will be generated to support regulatory filings and updates.

7.14 Changes in the Statistical Analysis Plan

Change from protocol

Proportion of subjects with clinical response during long-term vedolizumab SC treatment using HBI scores in CD subjects will not be summarized in Scenario 2 and Scenario 3 due to data collection limitation.

Rationale for Change: CD disease activity are measured using two different indices in SC-3031 and SC-3030, CDAI and HBI respectively. For Scenario 2 and Scenario 3, the baseline in parent study SC-3031 are used for comparison which is not available.

Surgical intervention was not included in the treatment failure definition in the protocol but was included in the interim analysis SAP. To be consistent with the interim analysis SAP, surgical intervention is included in the treatment failure definition in this SAP.

7.14.1 Revision History

Version	Date	Description of Revision
1.0	05 JAN 2022	N/A
2.0	10 MAY 2022	Added additional analysis related to COVID-19 in section 7.3 Added imputation rule for Concomitant Medication in section 7.6 [redacted] Added imputation rule for Adverse Event in section 7.12.2 Added additional language for surgical intervention in section 7.14 Added that interim analysis and reports to be generated to support regulatory filings and updates
3.0	18 June 2024	Updated the Sections 7.1.5, 7.9.2.2, 7.12.2 and Table 7.a

8.0 REFERENCES

1. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. New Engl J Med 2005;353(23):2462-76.
2. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;315(8167):514.

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	--	>3 × ULN
AST	--	>3× ULN
GGT	--	>3× ULN
Alkaline phosphatase	--	>3× ULN
Total bilirubin	--	>2.0 mg/dL
Albumin	<2.5 g/dL	--
Total protein	<0.8x LLN	>1.2× 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	--	>5× 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 HBI for the Assessment of Crohn's Disease Activity

Adapted from: Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980; 1 (8167):514.

Appendix E 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
	Romania	Serbia	Slovak Republic
Eastern Europe	Bosnia and Herzegovina	Bulgaria	Croatia
	Estonia	Israel	Russia
	Turkey	Ukraine	
East Asia	Japan	Republic of Korea	
Africa / Australia	Australia	South Africa	

Appendix F 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
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 G Prior Therapies

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

Appendix H 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/CD	Percentage of work time missed because of UC/CD in the past seven days	Q2/(Q2+Q4)
	Percentage of impairment experienced while at work in the past seven days because of UC/CD	Q5/10
	Overall work productivity loss	Q2/(Q2+Q4)+ [(1- Q2/(Q2+Q4))×Q5/10]
	Percentage of impairment in daily activities due to UC/CD in the past 7 days	Q6/10

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