



Title: Phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and pharmacokinetics of intravenous MLN0002 (300 mg) infusion in induction and maintenance therapy in Japanese subjects with moderate or severe ulcerative colitis

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Note; This document was translated into English as the language on original version was Japanese.

STATISTICAL ANALYSIS PLAN (Induction Phase)

Study Title : Phase 3, multicenter, randomized, double-blinded,
placebo-controlled, parallel-group study to evaluate the efficacy,
safety, and pharmacokinetics of intravenous MLN0002 (300 mg)
infusion in induction and maintenance therapy in Japanese subjects
with moderate or severe ulcerative colitis

Protocol No. : MLN0002/CCT-101

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	3
HANDLING OF TIME WINDOW	4
OTHER HANDLING	6
1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS	12
1.1 Disposition of Subjects	12
1.1.1 Study Information	12
1.1.2 Disposition of All Subjects Who Did Not Enter in the Induction Phase	12
1.1.3 Subject Eligibility	12
1.1.4 Number of Subjects Who Entered in the Induction Phase by Site	12
1.1.5 Disposition of Subjects	13
1.1.5.1 Disposition of Subjects	13
1.1.6 Study Drug Completion Status and Study Visit Completion Status	14
1.1.7 Protocol Deviations and Analysis Sets	15
1.2 Demographic and Other Baseline Characteristics.....	17
1.2.1 Distribution of Baseline Demographics.....	17
1.2.2 Medical History, Concurrent Medical Conditions.....	18
1.2.3 Medication History, Concomitant Medications in the Induction Phase, Concomitant Therapies in the Induction Phase.....	19
1.3 Measurement of Compliance Status for Treatment	21
1.3.1 Study Drug Exposure and Compliance in the Induction Phase	21
2 EFFICACY ANALYSIS	23
2.1 Primary Endpoints and Analysis Methodology	23
2.1.1 Primary Analysis.....	23
2.1.2 Secondary Analysis.....	23
2.2 Secondary Endpoints and Analysis Methodology	24
2.3 Other Endpoints and Analysis Methodology	27
2.3.1 Endpoints Related to Mayo Scores	27
2.3.2 Endpoints Related to IBDQ	30
2.4 Analysis in the Cohort 2	32
2.5 Statistical and Analytical Issues.....	33
2.5.1 Adjustments for Covariates.....	33
2.5.2 Handling of Dropouts or Missing Data.....	34
2.5.3 Interim Analyses and Data Monitoring.....	34
2.5.4 Multicenter Studies	34
2.5.5 Multiple Comparisons/Multiplicity.....	34
2.5.6 Use of an “Efficacy Subset of Subjects”.....	35
2.5.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority	35
2.5.8 Examination of Subgroups.....	35
3 SAFETY ANALYSIS.....	37

3.1 Treatment-Emergent Adverse Event.....	37
3.1.1 Overview of Treatment-Emergent Adverse Events	37
3.1.2 Displays of Treatment-Emergent Adverse Events.....	38
3.2 Pretreatment Event.....	40
3.2.1 Displays of Pretreatment Events.....	40
3.3 Clinical Laboratory Evaluations and Other Safety Endpoints	40
3.3.1 Clinical Laboratory Evaluations	40
3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety	42
3.4 Display of Treatment-Emergent Adverse Event (in Japanese).....	43
4 PHARMACOKINETIC ANALYSIS	44
4.1 Analysis of Serum Concentrations of MLN0002.....	44
4.2 Serum Concentrations of MLN0002 by Efficacy Endpoints	44
4.3 Serum Concentrations of MLN0002 by AVA and Neutralizing Antibody.....	44
4.4 Efficacy by Serum Concentration of MLN0002.....	45
5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS.....	47
5.1 AVA and Neutralizing Antibody	47
5.2 Efficacy by AVA and Neutralizing Antibody.....	47
5.3 AVA and Neutralizing Antibody by Concomitant Use of Immunomodulators.....	48
6 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT	49
History of Revision (version management)	50
[Appendix 1] Comparison Table for Changes	1
[Appendix 2] Definitions of Categories in Shift Table, MAV Criteria, and Criteria for Elevated Liver Enzyme	1

Since the study has different objectives in the induction phase, the maintenance phase and the open-label cohort, analyses will be conducted separately among these. Therefore, the “Statistical Analysis Plan” will be also prepared for the induction phase, maintenance phase, and open-label cohort respectively. This statistical analysis plan will describe the analytical plan in the induction phase.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

- Treatment-emergent adverse event (TEAE) in the induction phase: An adverse event that emerged during the induction phase.
- All subjects entered in the induction phase: All subjects who were allocated in the Cohort 1 or Cohort 2 in the induction phase.
- Concomitant medication in the induction phase: Any concomitant medication which was started by the day before the first dose of the study drug in the maintenance phase or open-label cohort (whichever comes first if both events occur) for subjects who received the study drug in the maintenance phase or open-label cohort. “By the day before the first dose of the study drug in the maintenance phase or open-label cohort (whichever comes first if both events occur)” will include the day before the first dose of the study drug in the maintenance phase or open-label cohort. Hereinafter, the same expression (by -) will be interpreted in the same manner. For subjects who did not receive the study drug in the maintenance phase and open-label cohort, all concomitant medications are included.
- Concomitant therapy in the induction phase: Any concomitant therapy which was started by the day before the first dose of the study drug in the maintenance phase or open-label cohort (whichever comes first if both events occur) for subjects who received the study drug in the maintenance phase or open-label cohort. For subjects who did not receive the study drug in the maintenance phase and open-label cohort, all concomitant therapies are included.
- Summary statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- MAV: An abbreviation for markedly abnormal value.
- Study Day: The day before the first dose of the study drug in the induction phase will be defined as Day -1 and the day of the first dose in the induction phase will be defined as Day 1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1. There will be no distinction among the induction phase, maintenance phase, and open-label cohort for the day of the last dose of the study drug.
- Full analysis set in the induction phase: Subjects who were randomized and received at least one dose of the study drug in the induction phase. The full analysis set in the induction phase does not include subjects allocated in the Cohort 2 in the induction phase.
- Per protocol set in the induction phase: All subjects in full analysis set in the induction phase who did not have any major protocol deviations, have met the minimum protocol provisions, and have evaluable primary endpoint(s).
- Safety analysis set in the induction phase: Subjects who received at least one dose of the study drug in the induction phase (Cohort 1 and Cohort 2).

- Cohorts and treatment groups in the induction phase: MLN0002 group, placebo group, and Cohort 2.
- Treatment groups in the induction phase: MLN0002 group and placebo group
- Anti-vedolizumab antibody (AVA): Human anti-human antibody (HAHA) in the protocol will be described as AVA.

HANDLING OF TIME WINDOW

For each test, observation, and evaluation item, evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) will be handled according to the following rules.

For acceptable windows at each visit except for Week 0, the evaluable data within the acceptable window for subjects who received the study drug in the maintenance phase or open-label cohort will be used among the data measured prior to the day of the first dose of the study drug in the maintenance phase or open-label cohort. The evaluable data within the acceptable window will be used for other subjects. If more than one datum lies within the same acceptable window, the data whose test/observation/evaluation date is closest to the scheduled date will be used and, if there are two data equidistant to the scheduled date, the data obtained later will be used. The temporal distance from the scheduled date will be determined based on the Study Day and Follow-up Day. If the date of the first dose of the study drug in the maintenance phase or open-label cohort is smaller than the lower limit of the acceptable window in the table, the acceptable window at that visit will not be applied.

Complete Mayo score*¹, Mayo subscore (findings on endoscopy)*², IBDQ score (total score and each subscore (abdominal symptoms, general condition, emotion, and social function))

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	

*¹ Clinical response and clinical remission will be determined based on complete Mayo scores.

*² Mucosal healing will be determined based on Mayo subscores (findings on endoscopy).

Partial Mayo score*¹, Mayo subscore (stool frequency, rectal bleeding, physician’s global assessment)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 2	Study Day: 15	2 to 28	
Week 6	Study Day: 43	29 to 56	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 10	Study Day: 71	57 to 84	

*¹ Clinical response based on partial Mayo score will be determined based on partial Mayo scores.

Vital signs, body weight

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 2	Study Day: 15	2 to 28	
Week 6	Study Day: 43	29 to 56	
Week 10	Study Day: 71	57 to 84	
Week 14	Study Day: 99	85 to 112	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the maintenance phase and open-label cohort.

Laboratory tests (hematology, blood biochemistry, inflammatory markers)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 2	Study Day: 15	2 to 28	
Week 6	Study Day: 43	29 to 56	
Week 10	Study Day: 71	57 to 84	
Week 14	Study Day: 99	85 to 126	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the maintenance phase and open-label cohort. Not applied to laboratory test (inflammatory markers).

Laboratory test (urinalysis)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	
Week 14	Study Day: 99	85 to 126	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the maintenance phase and open-label cohort.

12-lead ECG, AVA, neutralizing antibody

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the maintenance phase and open-label cohort.

Serum concentrations of MLN0002

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 2* ¹	Study Day: 15	12 to 18	
Week 6* ¹	Study Day: 43	40 to 46	
Week 10	Study Day: 71	68 to 74	
Week 14* ¹	Study Day: 99	92 to 106	

*¹ For Week 2, Week 6, and Week 14, only data measured from 3 hours before administration until immediately before administration will be used.

OTHER HANDLING

In principle, if any variable value used for calculation or adjudication is missing, the result of the calculation or adjudication will be handled as missing. If other handling of missing data is described, follow that handling.

- Duration of study drug exposure in the induction phase (day): Date of the last dose of the study drug in the induction phase – date of the first dose of the study drug in the induction phase + 1
- Duration on study after the first dose of the study drug in the induction phase (day): For subjects who received the study drug in the maintenance phase or open-label cohort, “(the smallest date in the maintenance phase or open-label cohort unless date of the first dose of the study drug is missing) – date of the first dose of the study drug in the induction phase” and for other subjects, “date of last visit or contact – date of the first dose of the study drug in the induction phase + 1”
- BMI (kg/m²) = Weight (kg) / (Height [cm]/100)² (round off to the first decimal place)
- Duration of UC (year): (Date of informed consent [year and month] – Date of UC diagnosis [year and month]) / 12 (round off to the first decimal place)
 - Only year and month for date of informed consent will be used.
 - The unit for “Date of informed consent (year and month) – Date of UC diagnosis (year and month)” will be “months.”
 - If the year of UC diagnosis is unknown, the duration of UC will be handled as “Missing.” If only the month of UC diagnosis is unknown, the duration of UC will be calculated by setting the month of UC diagnosis as January.
- Prior corticosteroids failure: If corticosteroids resistance, dependence, or intolerance is “Yes,” prior corticosteroids failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Classification 1 of prior corticosteroids failure: Subjects for whom prior corticosteroid failure is “Yes” are classified as follows:
 - Subjects for whom corticosteroid resistance is “Yes” are classified as “Resistance.”
 - Among subjects for whom corticosteroids resistance is not “Yes,” subjects for whom corticosteroid dependence is “Yes” are classified as “Dependence.”
 - Among subjects for whom corticosteroids resistance is not “Yes” as well as corticosteroid dependence not being “Yes,” subjects for whom corticosteroid intolerance is “Yes” are classified as “Intolerance.”
- Classification 2 of prior corticosteroids failure: Subjects for whom prior corticosteroid failure is “Yes” are classified as follows:
 - Subjects for whom corticosteroid resistance is “Yes” or corticosteroid dependence is “Yes” are classified as “Refractory.”
 - Among subjects for whom corticosteroids resistance is not “Yes” as well as corticosteroid dependence not being “Yes,” subjects for whom corticosteroid intolerance is “Yes” are classified as “Intolerance.”
- Prior immunomodulators failure: If either of immunomodulator refractory or intolerance is “Yes,” prior immunomodulators failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Classification of prior immunomodulators failure: Subjects for whom prior immunomodulators failure is “Yes” are classified as follows:
 - Subjects for whom immunomodulator refractory is “Yes” are classified as “Refractory.”

- Among the subjects for whom immunomodulator refractory are not “Yes,” subjects for whom immunomodulatory intolerance is “Yes” are classified as “Intolerance.”
- Prior TNF α antagonist failure: If inadequate response, loss of response, or intolerance to the TNF α antagonist is “Yes,” prior TNF α antagonist failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Number of drugs of TNF α antagonist failure: Among the drugs entered to prior treatment failure (TNF α antagonist) for UC, subjects whose Who Drug is coded with 1 type of drug with Preferred Name are classified as “Treatment failure with 1 drug.” Similarly, subjects who are coded with 2 types of drugs are classified as “Treatment failure with 2 drugs” and subjects who are coded with 3 types of drugs as “Treatment failure with 3 drugs.” Subjects who are not coded with any drug in the prior treatment failure (TNF α antagonist) for UC are classified as “No.”
- Classification of prior TNF α antagonist failure: Subjects for whom TNF α antagonist failure is “Yes” are classified as follows:
 - Subjects for whom TNF α antagonist inadequate response is “Yes” are classified as “Inadequate response.”
 - Among subjects for whom TNF α antagonist inadequate response was not “Yes,” subjects for whom TNF α antagonist loss of response was “Yes” are classified as “Loss of response.”
 - Among subjects for whom TNF α antagonist inadequate response is not “Yes” as well as TNF α antagonist loss of response not being “Yes,” subjects for whom TNF α antagonist intolerance is “Yes” are classified as “Intolerance.”
- Prior immunomodulators failure (excluding prior TNF α antagonist failure): If prior TNF α antagonist failure is “No” and prior immunomodulators failure is “Yes,” prior immunomodulators failure (excluding prior TNF α antagonist failure) will be defined as “Yes.” All others will be defined as “No.”
- Prior corticosteroid failure only: If prior TNF α antagonist failure is “No,” prior immunomodulators failure is “No,” and prior corticosteroids failure is “Yes,” prior corticosteroid failure only will be defined as “Yes.” All others will be defined as “No.”
- Prior immunomodulators and TNF α antagonist failure: If prior immunomodulators failure is “Yes” and prior TNF α antagonist failure is “Yes,” prior immunomodulators and TNF α antagonist failure will be defined as “Yes.” All others will be defined as “No.”
- Completion of the study drug infusion: If the infusion of the study drug is “Completed” or dose of the study drug is ≥ 79 mL (percentage of dose against prepared study drug of 105 mL is $\geq 75\%$), the study drug infusion will be defined as “Completed.” All others will be defined as “Incompleted.”

Mayo score will be handled as follows:

- Complete Mayo score: Sum of each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy, and physician’s global assessment).
 - The complete Mayo score will be calculated using subscores on the same day of evaluation. The day of evaluation for stool frequency and rectal bleeding will be the same as the day

of evaluation for physician's global assessment.

- If any Mayo subscore is missing, the complete Mayo score will be handled as missing.
- Clinical response: If the following 2 conditions are fulfilled, subjects will be classified as "Clinical response." All others will be classified as "Non-response." However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing "HANDLING OF TIME WINDOW," subjects will be classified as "Non-response."
 - Decrease of the complete Mayo score by ≥ 3 points and by $\geq 30\%$ from baseline (Week 0)
 - Decrease of the subscore of rectal bleeding by ≥ 1 point from baseline (Week 0) or ≤ 1 in the subscore of rectal bleeding
- Clinical remission: If the complete Mayo score is ≤ 2 and all subscores are ≤ 1 , subjects will be classified as "Clinical remission." All others will be classified as "Non-remission." However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing "HANDLING OF TIME WINDOW," subjects will be classified as "Non-remission."
- Mucosal healing: If the subscore for the findings on endoscopy is ≤ 1 , subjects will be classified as "Mucosal healing." All others will be classified as "Non-healing." However, if any of the scores used for adjudication are missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing "HANDLING OF TIME WINDOW," subjects will be classified as "Non-healing."
- 0 in the subscore for the findings on endoscopy: "Yes" if the subscore for the findings on endoscopy is 0 and "No" if it is ≥ 1 or missing.
- Partial Mayo score: Sum of subscores for stool frequency, rectal bleeding, and physician's global assessment.
 - The partial Mayo score will be calculated using subscores on the same day of measurement. The day of evaluation for stool frequency and rectal bleeding will be the same as the day of evaluation for physician's global assessment.
 - If any of the subscores for stool frequency, rectal bleeding, and physician's global assessment used for calculation of the partial Mayo score are missing, the partial Mayo score will be handled as missing.
- Clinical response based on partial Mayo score: If the following 2 conditions are fulfilled, subjects will be classified as "Clinical response based on partial Mayo score." All others will be classified as "Non-response based on partial Mayo score." However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing "HANDLING OF TIME WINDOW," subjects will be classified as "Non-response based on partial Mayo score."
 - Decrease of the partial Mayo score by ≥ 2 points and by $\geq 25\%$ from baseline (Week 0)
 - Decrease of the subscore of rectal bleeding by ≥ 1 point from baseline(Week 0) or ≤ 1 in the subscore of rectal bleeding

IBDQ score will be handled as follows:

- The questions (Q) on the same day of measurement will be used for calculation of each subscore and total score. After calculating each subscore and total score, the time point will be transferred.
- IBDQ subscore for abdominal symptoms: Mean of Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29 (round off to the first decimal place).
- IBDQ subscore for general condition: Mean of Q2, Q6, Q10, Q14, and Q18 (round off to the first decimal place).
- IBDQ subscore for emotion: Mean of Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31, and Q32 (round off to the first decimal place).
- IBDQ subscore for social function: Mean of Q4, Q8, Q12, Q16, and Q28 (round off to the first decimal place).
- IBDQ total score: Sum of all questions (round off to the first decimal place).
 - The value of each question after imputing missing data will be used for the calculation of each subscore (abdominal symptoms, general condition, emotion, and social function).
- The handling of missing data in calculation of each subscore (abdominal symptoms, general condition, emotion, and social function) and IBDQ total score will be defined as follows:

Variable	Handling of missing data
IBDQ subscore for abdominal symptoms, IBDQ subscore for general condition, IBDQ subscore for emotion, and IBDQ subscore for social function	<ul style="list-style-type: none"> • If 1 question is missing among those used for calculation of each subscore, the missing data will be imputed using the mean of the non-missing questions used for calculation of that subscore. • If 2 questions are missing among those used for calculation of each subscore, that subscore will be handled as missing.
IBDQ total score	<ul style="list-style-type: none"> • Among the questions used for calculation of IBDQ total score, the missing data will be imputed using the mean of the non-missing questions used for calculation of each subscore. However, if 5 or more questions are missing or more than 2 subscores are missing among the questions used for calculation of IBDQ total score or 3 or more questions are missing among those used for calculation of a certain subscore, the total score will be handled as missing.

- 170 or higher in IBDQ total score: “Yes” if IBDQ total score is ≥ 170 , “No” if it is < 170 , and “Missing” if it is missing.
- 16 or higher in change from baseline (Week 0) in IBDQ total score: “Yes” if the change from baseline (Week 0) in IBDQ total score is ≥ 16 , “No” if it is < 16 , and “Missing” if it is missing.
- -16 or lower in change from baseline (Week 0) in IBDQ total score: “Yes” if the change from baseline (Week 0) in IBDQ total score is ≤ -16 , “No” if it is > -16 , and “Missing” if it is missing.

A prior TNF α antagonist use, concomitant use of immunomodulators at Week 0, and concomitant use of oral corticosteroids at Week 0 will be defined as follows:

- Prior TNF α antagonist use: Subjects coded with at least 1 drug of Preferred Name of Who Drug in the following table for medication history will be classified as “Yes.” All others will be classified as “No.”

Preferred Name
Infliximab
Adalimumab
Golimumab

- Concomitant use of immunomodulators at Week 0: Subjects who received any concomitant medication (for treatment of UC) which is classified as “immunomodulator” in the concomitant medication (for treatment of UC) which was started before the first dose of the study drug in the induction phase and continued in the induction phase will be classified as “Yes.” All others will be classified as “No.”
 - Any concomitant medication (for treatment of UC) which was started after the first dose of the study drug in the induction phase is not subject to this handling.
- Concomitant use of oral corticosteroids at Week 0: Subjects who received any concomitant medication (for treatment of UC) which is classified as “corticosteroid” and whose route of administration is “oral” in the concomitant medication (for treatment of UC) which was started before the first dose of the study drug in the induction phase and continued in the induction phase will be classified as “Yes.” All others will be classified as “No.”
 - Any concomitant medication (for treatment of UC) which was started after the first dose of the study drug in the induction phase is not subject to this handling.

Negative or positive status of the neutralizing antibody will be determined as follows:

- “Positive” if the neutralizing antibody is positive for AVA and neutralizing antibody with the same VISIT in each subject. “Negative” if the neutralizing antibody is negative or AVA is negative. Neutralizing antibody will be handled as missing if it does not correspond to any of the above.

Lymphocytes and neutrophils will be calculated with the following formula:

- Lymphocytes = WBC \times lymphocytes (%)
- Neutrophils = WBC \times neutrophils (%)

1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS

1.1 Disposition of Subjects

1.1.1 Study Information

Analysis set:	All subjects who signed the informed consent form
Analysis variables:	Date first subject signed the informed consent form MedDRA version WHO Drug version SAS version used for creating the datasets
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Display of the analysis variables

1.1.2 Disposition of All Subjects Who Did Not Enter in the Induction Phase

Analysis set:	All subjects who did not enter in the induction phase
Analysis variables:	Categories in parenthesis [] (hereinafter the same) Age (years) [Min≤ - ≤34, 35≤ - ≤Max] [Min≤ - ≤64, 65≤ - ≤Max] Gender [Male, Female]
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.1.3 Subject Eligibility

Analysis set:	All subjects who signed the informed consent form
Analysis variables:	Eligibility for entering into the induction phase [Eligible, Not eligible] Reason for being not eligible for entering into the induction phase [Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Did not meet entrance criteria, Other]
Analysis methodology:	The following analysis will be performed for the above analysis variables. When calculating percentages of the reasons for not being eligible for entering into the induction phase, the total number of ineligible subjects in the induction phase will be used as the denominator. (1) Frequency distributions

1.1.4 Number of Subjects Who Entered in the Induction Phase by Site

Analysis set:	All subjects who entered in the induction phase
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Analysis variables:	Eligibility for entering into the induction phase	[Eligible]
Stratum:	Study site	[Site numbers will be used as categories]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”	
	(1) Frequency distributions	

1.1.5 Disposition of Subjects

1.1.5.1 Disposition of Subjects

Analysis set:	All subjects who entered in the induction phase	
Analysis variables:	Study drug administration status in the induction phase	[Not treated]
	Reason for not being treated	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study drug completion status in the induction phase	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study visit completion status in the induction phase	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.” When calculating percentages of the reasons for not being treated, the total number of subjects not treated by the study drug in the induction phase will be used as the denominator. When calculating percentages of the reasons for not being	

completed, the total number of subjects who did not completed the study drug/study visit in the induction phase will be used as the denominator.

(1) Frequency distributions

1.1.6 Study Drug Completion Status and Study Visit Completion Status

Analysis set:	All subjects who entered in the induction phase	
Analysis variables:	Study drug completion status	[Completed, Incompleted]
	in the induction phase	
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study visit completion status	[Completed, Incompleted]
	in the induction phase	
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Categories:	Duration of study drug exposure in the induction phase (days)	[0, 1≤ - ≤28, 29≤ - ≤56, 57≤ - ≤Max]
	Duration on study after the first dose of the study drug in the induction phase (days)	[0, 1≤ - ≤28, 29≤ - ≤56, 57≤ - ≤84, 85≤ - ≤Max]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”	
	Frequency distributions will be provided for study drug completion status in the induction phase in the analysis of (1). Frequency distributions will be provided for study visit completion status in the induction phase in the analysis of (2).	
	(1) Frequency distribution by duration of study drug exposure in the induction phase	
	(2) Frequency distribution by duration on study after the first dose of the study drug in the induction phase	

1.1.7 Protocol Deviations and Analysis Sets

1.1.7.1 Protocol Deviations in the Induction Phase

Analysis set:	All subjects who entered in the induction phase	
Analysis variables:	Protocol deviations in the induction phase	[Major GCP violations, Deviations of protocol entry criteria, Deviations of discontinuation criteria, Deviations related to treatment procedure or dose, Deviations concerning excluded medication or therapy, Deviations to avoid emergency risk, Other]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.” Frequency distribution of subjects with protocol deviations in the induction phase will be provided for above each deviation category. A subject who has several deviations that can be classified into the same category will be counted once in each appropriate category (overlapped counting). (1) Frequency distributions	

1.1.7.2 Analysis Sets of All Subjects Randomized in the Induction Phase

Analysis set:	All subjects randomized in the induction phase	
Analysis variables:	Handling of subjects and subject data in the induction phase in analysis sets	[Categories are based on the specifications in “Handling Rules for Analysis Data”]
	Inclusion/Exclusion of analysis sets	
	Full analysis set in the induction phase	[Included]
	Per protocol set in the induction phase	[Included]

Analysis methodology: The following analyses of (1) and (2) will be performed for the above analysis variables by treatment group in the induction phase and the following analysis of (3) will be performed by treatment group in the induction phase and in the consolidated treatment group in the induction phase.

A subject who corresponds to several categories in (1) and (2) will be counted once in each appropriate category (overlapped counting).

- (1) Frequency distributions concerning the handling of subjects in the induction phase in each analysis set
- (2) Frequency distributions concerning the handling of subject data in the induction phase in each analysis set
- (3) Frequency distributions concerning the number of subjects included in each analysis set

1.1.7.3 Analysis Sets of All Subjects Who Entered in the Induction Phase

Analysis set: All subjects who entered in the induction phase

Analysis variables: Handling of subjects and subject data in the induction phase in analysis sets [Categories are based on the specifications in “Handling Rules for Analysis Data”]

Inclusion/Exclusion of analysis sets

Safety analysis set in the induction phase [Included]

Analysis methodology: The following analyses of (1) and (2) will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and the following analysis of (3) will be performed by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”

A subject who corresponds to several categories in (1) and (2) will be counted once in each appropriate category (overlapped counting).

- (1) Frequency distributions concerning the handling of subjects in the induction phase in each analysis set
- (2) Frequency distributions concerning the handling of subject data in the induction phase in each analysis set
- (3) Frequency distributions concerning the number of subjects included in each analysis set

1.2 Demographic and Other Baseline Characteristics

1.2.1 Distribution of Baseline Demographics

Analysis set:	All subjects who entered in the induction phase	
Analysis variables:	Age (years)	[Min≤ - ≤34, 35≤ - ≤Max] [Min≤ - ≤64, 65≤ - ≤Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg) at Week 0	[Min≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
	BMI (kg/m ²) at Week 0	[Min≤ - ≤18.4, 18.5≤ - ≤24.9, 25.0≤ - ≤Max]
	Smoking classification	[Never smoked, Current smoker, Ex-smoker]
	Duration of UC (years)	[Min≤ - <1, 1≤ - <3, 3≤ - <7, 7≤ - ≤Max, Missing]
	Prior corticosteroids failure	[Yes, No]
	Classification 1 of prior corticosteroids failure	[Resistance, Dependence, Intolerance]
	Classification 2 of prior corticosteroids failure	[Refractory, Intolerance]
	Prior immunomodulators failure	[Yes, No]
	Classification of prior immunomodulators failure	[Refractory, Intolerance]
	Prior TNF α antagonist failure	[Yes, No]
	Number of drugs of TNF α antagonist failure	[1 drug, 2 drugs, 3 drugs, None]
	Classification of prior TNF α antagonist failure	[Inadequate response, Loss of response, Intolerance]
	Worst prior treatment failures	[Prior TNF α antagonist failure, Prior immunomodulators failure but not TNF α antagonist failure, Prior corticosteroid failure only]
	Prior immunomodulators and TNF α antagonist failure	[Yes, No]
	Prior TNF α antagonist use	[Yes, No]
	Infliximab	[Yes, No]
	Adalimumab	[Yes, No]
	Golimumab	[Yes, No]
	Concomitant use of 5-ASA at	[Yes, No]

Week 0	
Concomitant use of immunomodulators at Week 0	[Yes, No]
Concomitant use of oral corticosteroids at Week 0	[Yes, No]
No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0	[Yes, No]
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0 (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0	[Yes, No]
Complete Mayo score at Week 0	[0 ≤ - ≤5, 6 ≤ - ≤8, 9 ≤ - ≤12]
Disease localization	[Total colitis, Left-sided colitis]
Concurrent extraintestinal manifestations	[Yes, No]

Analysis methodology: The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”

- (1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.2.2 Medical History, Concurrent Medical Conditions

Analysis set: Safety analysis set in the induction phase
 Analysis variables: Medical history
 Concurrent medical conditions (concurrent extraintestinal

manifestations of UC)

Concurrent medical conditions (other than concurrent extraintestinal manifestations of UC)

Analysis methodology: The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”

The analysis variables will be coded by use of MedDRA and will be summarized based on the SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

- (1) Frequency distributions for medical history (by SOC and PT)
- (2) Frequency distributions for concurrent medical conditions (concurrent extraintestinal manifestations of UC) (by SOC and PT)
- (3) Frequency distributions for concurrent medical conditions (other than concurrent extraintestinal manifestations of UC) (by SOC and PT)

The method of counting events when providing each frequency distribution will be as follows:

[Number of subjects]

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

1.2.3 Medication History, Concomitant Medications in the Induction Phase, Concomitant Therapies in the Induction Phase

Analysis set:	Safety analysis set in the induction phase
Analysis variables:	Medication history
	Concomitant medications (for treatment of UC) in the induction phase
	Classification of concomitant medications (for treatment of UC) in the induction phase
	[5-ASA, Corticosteroids, Immunomodulators, Other]
	Concomitant medications (for treatment of UC) in the induction phase that fall under the category of rescue treatments
	Classification of concomitant
	[5-ASA,

medications (for treatment of UC) in the induction phase that fall under the category of rescue treatments Corticosteroids, Immunomodulators, Other]

Concomitant medications (for other than treatment of UC) in the induction phase

Concomitant therapies in the induction phase [Yes, No]

Concomitant therapies in the induction phase that fall under the category of rescue treatments [Yes, No]

Analysis methodology: The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”

Medication history, concomitant medications (for treatment of UC) in the induction phase, concomitant medications (for treatment of UC) in the induction phase that fall under the category of rescue treatments, and concomitant medications (for other than treatment of UC) in the induction phase will be coded by use of WHO Drug and summarized based on Preferred Name, which will be sorted in decreasing frequency.

A subject who has been administered several medications with the same Preferred Name will be counted only once for that Preferred Name.

- (1) Frequency distributions for medication history
- (2) Frequency distributions for concomitant medications (for treatment of UC) in the induction phase that were ongoing at baseline and continued in the induction phase, and concomitant medications (for treatment of UC) in the induction phase that started after baseline by category
- (3) Frequency distributions for concomitant medications (for treatment of UC) in the induction phase that fall under the category of rescue treatments that were ongoing at baseline and continued in the induction phase, and concomitant medications (for treatment of UC) in the induction phase that fall under the category of rescue treatments and started after baseline by category
- (4) Frequency distributions for concomitant medications (for other than treatment of UC) in the induction phase that were ongoing at baseline and continued in the induction phase and concomitant medications (for other than treatment of UC) in

the induction phase that started after baseline

- (5) Frequency distributions for presence or absence of concomitant therapies in the induction phase that were ongoing at baseline and continued in the induction phase and concomitant therapies in the induction phase that started after baseline
- (6) Frequency distributions for presence or absence of concomitant therapies in the induction phase that fall under the category of rescue treatments that were ongoing at baseline and continued in the induction phase and concomitant therapies in the induction phase that fall under the category of rescue treatments and started after baseline

1.3 Measurement of Compliance Status for Treatment

1.3.1 Study Drug Exposure and Compliance in the Induction Phase

Analysis set:	Safety analysis set in the induction phase	
Analysis variables:	Duration of study drug exposure in the induction phase (days)	[1 ≤ - ≤28, 29 ≤ - ≤56, 57 ≤ - ≤Max]
	Duration on study after the first dose of the study drug in the induction phase (days)	[1 ≤ - ≤28, 29 ≤ - ≤56, 57 ≤ - ≤84, 85 ≤ - ≤Max]
	Number of the study drug infusion in the induction phase (times)	[1, 2, 3]
	Number of completed infusions of the study drug in the induction phase (times)	[0, 1, 2, 3]
	Number of completed or incompleted infusions in total infusions in the induction phase	[Completed, Incompleted]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”	
	(1) Frequency distributions for categorical variables and summary statistics for continuous variables	
	In the frequency distributions for number of completed or incompleted infusions in total infusions in the induction phase, the sum of the number of completed infusions in the induction phase in the applicable treatment group will be counted as frequency for “Completed” and the sum of the number of incompleted infusions will be counted as frequency for “Incompleted.” When calculating	

percentage, the sum of the number of completed infusions and the number of incompletd infusions (i.e., number of total infusions in the induction phase) will be used as the denominator.

2 EFFICACY ANALYSIS

The “full analysis set in the induction phase” based on the specifications in the protocol and the “Handling Rules for Analysis Data” will be the main analysis set. For the sensitivity point of view, the “per protocol set in the induction phase” will be used for an analysis performed secondarily on the primary endpoint in order to examine the robustness of the results.

2.1 Primary Endpoints and Analysis Methodology

2.1.1 Primary Analysis

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	Clinical response at Week 10	[Clinical response, Non-response]
Stratum:	Prior TNF α antagonist use	[Yes, No]
Analysis methodology:	The following analysis will be performed in the “full analysis set in the induction phase.” Frequency distributions will be provided for “clinical response at Week 10” (the primary endpoint of the induction phase) by treatment group in the induction phase along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated. The similar calculation will be performed with stratification according to the “prior TNF α antagonist use.” The Cochran-Mantel-Haenszel (CMH) test will be performed using the “prior TNF α antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy.	

The results of the primary analysis of the induction phase will be interpreted as below to determine the efficacy of MLN0002 induction therapy.

- The superiority of MLN0002 over the placebo on clinical response at Week 10 in the primary analysis of the induction phase will be demonstrated when a statistically significant difference is observed in the clinical response at Week 10.

2.1.2 Secondary Analysis

Analysis set:	Full analysis set in the induction phase Per protocol set in the induction phase	
Analysis variables:	Clinical response at Week 10	[Clinical response,

		Non-response]
Stratum:	Prior TNF α antagonist use	[Yes, No]
Analysis methodology:	For the sensitivity point of view, the following analysis will be performed to examine the robustness of the results.	
	(1) The clinical response at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site will be analyzed in the same manner as those in the primary analysis in 2.1.1 in the “per protocol set in the induction phase.”	
	(2) The clinical response at Week 10 using the scores of findings on endoscopy based on adjudication of the Clinical Endpoint Committee (CEC) will be analyzed in the same manner as those in the primary analysis in 2.1.1 in the “full analysis set in the induction phase.”	

The following analysis will be performed for reference.

- (3) For the clinical response at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site, the CMH adjusted risk difference (MLN0002 group – placebo group) with the “prior TNF α antagonist use” as a stratification factor and the 95% two-sided CI will be calculated in the “full analysis set in the induction phase.”
- (4) The clinical response at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site will be analyzed in the same manner as those in the primary analysis in 2.1.1 in the “full analysis set in the induction phase” after excluding the subjects whose complete Mayo scores at Week 10 are missing.

2.2 Secondary Endpoints and Analysis Methodology

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	Clinical remission at Week 10	[Clinical remission, Non-remission]
	Mucosal healing at Week 10	[Mucosal healing, Non-healing]
Stratum:	Prior TNF α antagonist use	[Yes, No]
Analysis methodology:	The following analysis will be performed for the above analysis variables by treatment group in the induction phase. The results of the secondary analysis of the induction phase will be interpreted as below to determine the efficacy of MLN0002 induction therapy.	

- The superiority of MLN0002 over the placebo on clinical remission at Week 10 will be demonstrated when statistically significant differences are observed in the clinical response at Week 10 in the primary analysis of 2.1.1 and the clinical remission at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site in the analysis methodology (3).
- (1) Frequency distributions will be provided for clinical remission at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
 - (2) Frequency distributions will be provided for clinical remission at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site with the “prior TNF α antagonist use” as a stratification factor along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
 - (3) The CMH test will be performed for clinical remission at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site with the “prior TNF α antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. Also, the CMH adjusted risk difference (MLN0002 group – placebo group) with the “prior TNF α antagonist use” as a stratification factor and the 95% two-sided CI will be calculated.
 - (4) Frequency distributions will be provided for clinical remission at Week 10 using the scores for the findings on endoscopy based on adjudication of the CEC along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
 - (5) Frequency distributions will be provided for clinical remission at Week 10 using the scores for the findings on endoscopy

based on adjudication of the CEC with the “prior TNF α antagonist use” as a stratification factor along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.

- (6) The CMH test will be performed for clinical remission at Week 10 using the scores for the findings on endoscopy based on adjudication of the CEC with the “prior TNF α antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI.
- (7) Frequency distributions will be provided for mucosal healing at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (8) Frequency distributions will be provided for mucosal healing at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site with the “prior TNF α antagonist use” as a stratification factor along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (9) The CMH test will be performed for mucosal healing at Week 10 using the scores of findings on endoscopy based on the adjudication results in the study site with the “prior TNF α antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. Also, the CMH adjusted risk difference (MLN0002 group – placebo group) with the “prior TNF α antagonist use” as a stratification factor and the 95% two-sided CI will be calculated.
- (10) Frequency distributions will be provided for mucosal healing at Week 10 using the scores for the findings on endoscopy based on adjudication of the CEC along with the point estimate and 95% two-sided CI for the proportion. The point

estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.

(11) Frequency distributions will be provided for mucosal healing at Week 10 using the scores for the findings on endoscopy based on adjudication of the CEC with the “prior TNF α antagonist use” as a stratification factor along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.

(12) The CMH test will be performed for mucosal healing at Week 10 using the scores for the findings on endoscopy based on adjudication of the CEC with the “prior TNF α antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI.

2.3 Other Endpoints and Analysis Methodology

2.3.1 Endpoints Related to Mayo Scores

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	Clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects without prior TNF α antagonist use and in the sub-population of subjects who had failed with a TNF α antagonist	[Clinical response, Non-response] [Clinical remission, Non-remission] [Mucosal healing, Non-healing]
	Clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects who had failed with a corticosteroid monotherapy and an immunomodulator (except those had failed with a TNF α antagonist)	[Clinical response, Non-response] [Clinical remission, Non-remission] [Mucosal healing, Non-healing]
	Partial Mayo score	
	Partial Mayo score change from baseline (Week 0)	
	Clinical response based on partial Mayo score	[Clinical response, Non-response]
	Complete Mayo score	

	Complete Mayo score change from baseline (Week 0)	
	Each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy, and physician's global assessment)	[0, 1, 2, 3]
	Change in each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy, and physician's global assessment) from baseline (Week 0)	
	0 in the subscore for the findings on endoscopy	[Yes, No]
Visit:	Weeks 0 and 10 (complete Mayo score, Mayo subscore [findings on endoscopy])	
	Week 10 ("Clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects without prior TNF α antagonist use and in the sub-population of subjects who had failed with a TNF α antagonist," "Clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects who had failed with a corticosteroid monotherapy and an immunomodulator [except those had failed with a TNF α antagonist],") Complete Mayo score change from baseline [Week 0], Mayo subscore [findings on endoscopy] change from baseline [Week 0], and 0 in the subscore for the findings on endoscopy)	
	Weeks 0, 2, 6, and 10 (partial Mayo score, each Mayo subscore (stool frequency, rectal bleeding, and physician's global assessment)	
	Weeks 2, 6, and 10 (partial Mayo score change from baseline [Week 0], change in each Mayo subscore [stool frequency, rectal bleeding, and physician's global assessment] from baseline [Week 0], clinical response based on partial Mayo score)	
Analysis methodology:	The following analysis will be performed for the above analysis variables by treatment group in the induction phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy for analyses (1) to (10).	
	(1) Frequency distributions will be provided for the clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects without prior TNF α antagonist use along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be	

also calculated.

- (2) Frequency distributions will be provided for the clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects who had failed with a TNF α antagonist along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (3) Frequency distributions will be provided for the clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects who had failed with a corticosteroid monotherapy along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (4) Frequency distributions will be provided for the clinical response, clinical remission, and mucosal healing at Week 10 in the sub-population of subjects who had failed with an immunomodulator (except those had failed with a TNF α antagonist) along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (5) Summary statistics and 95% two-sided CI of the mean will be calculated for partial Mayo scores at each visit.
- (6) Summary statistics and 95% two-sided CI of the mean will be calculated for partial Mayo score changes from baseline (Week 0) at each visit and also the point estimate and 95% two-sided CI for the difference in the mean between treatment groups (MLN0002 group – placebo group) will be calculated.
- (7) Frequency distributions will be provided for clinical response based on partial Mayo score at each visit along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (8) Summary statistics and 95% two-sided CI of the mean will be calculated for complete Mayo scores at each visit.

- (9) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in complete Mayo score at Week 10 from baseline (Week 0).
- (10) The point estimate and 95% two-sided CI for the difference in the least square (LS) mean between treatment groups (MLN0002 group – placebo group) will be calculated using the analysis of covariance (ANCOVA) model with changes in complete Mayo score at Week 10 from baseline (Week 0) as a response, the treatment groups in the induction phase, and “prior TNF α antagonist use” as factors, and complete Mayo score at Week 0 as a covariate.
- (11) Summary statistics and 95% two-sided CI of the mean will be calculated for each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy [adjudication results in the study site], findings on endoscopy [adjudication of the CEC], and physician’s global assessment) at each visit.
- (12) Summary statistics and 95% two-sided CI of the mean will be calculated for change in each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy [adjudication results in the study site], findings on endoscopy [adjudication of the CEC], and physician’s global assessment) from baseline (Week 0) at each visit.
- (13) Frequency distributions will be provided for each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy [adjudication results in the study site], findings on endoscopy [adjudication of the CEC], and physician’s global assessment) at each visit.
- (14) Frequency distributions will be provided for 0 in the subscore for the findings on endoscopy using the scores based on the adjudication results in the study site at Week 10 along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated. A similar analysis will be performed using the scores for the findings on endoscopy based on adjudication of the CEC.

2.3.2 Endpoints Related to IBDQ

Analysis set:	Full analysis set in the induction phase
Analysis variables:	IBDQ scores (total score and each subscore [abdominal symptoms, general condition,

emotion, and social function))

Change in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function]) from baseline (Week 0)

IBDQ total score ≥ 170 [Yes, No]

Change in IBDQ total score from baseline (Week 0) ≥ 16 [Yes, No]

Change in IBDQ total score from baseline (Week 0) ≤ -16 [Yes, No]

Visit:

Weeks 0 and 10 (IBDQ scores [total score and each subscore (abdominal symptoms, general condition, emotion, and social function)])

Week 10 (change in IBDQ score [total score and each subscore (abdominal symptoms, general condition, emotion, and social function)] from baseline (Week 0), IBDQ total score ≥ 170 , change in IBDQ total score from baseline (Week 0) ≥ 16 , and change in IBDQ total score from baseline (Week 0) ≤ -16)

Analysis methodology:

The following analysis will be performed for the above analysis variables by treatment group in the induction phase.

- (1) Summary statistics and 95% two-sided CI of the mean will be calculated for IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at each visit.
- (2) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 10 from baseline (Week 0).
- (3) The point estimate and 95% two-sided CI for the difference in the least square (LS) mean between treatment groups (MLN0002 group – placebo group) will be calculated using the analysis of covariance (ANCOVA) model with changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 10 from baseline (Week 0) as a response, the treatment groups in the induction phase as a factor, and baseline (Week 0) values that correspond to the scores used as response as a covariate.
- (4) Frequency distributions will be provided for subjects whose IBDQ total score at Week 10 is ≥ 170 among the subjects whose IBDQ total score at baseline (Week 0) is < 170 in the full analysis set in the induction phase along with the point

estimate and 95% two-sided CI for the proportion of subjects whose IBDQ total score is ≥ 170 . The point estimate and 95% two-sided CI for the difference in the proportion of subjects whose IBDQ total score is ≥ 170 between treatment groups (MLN0002 group – placebo group) will be calculated. The Pearson's chi-square test will be also performed.

- (5) Frequency distributions will be provided for subjects whose IBDQ total score change at Week 10 from baseline (Week 0) is ≥ 16 and subjects whose IBDQ total score change at Week 10 from baseline (Week 0) is ≤ -16 along with the point estimate and 95% two-sided CI for the proportion of subjects whose IBDQ total score change at Week 10 from baseline (Week 0) is ≥ 16 and proportion of subjects whose IBDQ total score change at Week 10 from baseline (Week 0) is ≤ -16 . The point estimate and 95% two-sided CI for the difference in the proportion of subjects whose IBDQ total score change at Week 10 from baseline (Week 0) is ≥ 16 and the proportion of subjects whose IBDQ total score change at Week 10 from baseline (Week 0) is ≤ -16 between treatment groups (MLN0002 group – placebo group) will be calculated. The Pearson's chi-square test will be also performed.

2.4 Analysis in the Cohort 2

Analysis set:	Subjects who were allocated in the Cohort 2 and received at least one dose of the study drug	
Analysis variables:	Clinical response at Week 10	[Clinical response, Non-response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
	Mucosal healing at Week 10	[Mucosal healing, Non-healing]
	Complete Mayo score	
	Complete Mayo score change from baseline (Week 0)	
	IBDQ score (total score)	
Visit:	IBDQ score (total score) change from baseline (Week 0)	
	Weeks 0 and 10 (IBDQ score [total score], complete Mayo score)	
	Week 10 (Complete Mayo score change from baseline [Week 0], IBDQ score [total score] change from baseline [Week 0])	

Analysis methodology: The following analysis will be performed for the above analysis variables. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy.

- (1) Frequency distributions will be provided for the clinical response at Week 10 along with the point estimate and 95% two-sided CI for the proportion.
- (2) Frequency distributions will be provided for the clinical remission at Week 10 along with the point estimate and 95% two-sided CI for the proportion.
- (3) Frequency distributions will be provided for mucosal healing at Week 10 along with the point estimate and 95% two-sided CI for the proportion.
- (4) Summary statistics and 95% two-sided CI of the mean will be calculated for complete Mayo scores at each visit.
- (5) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in complete Mayo score at Week 10 from baseline (Week 0).
- (6) Summary statistics and 95% two-sided CI of the mean will be calculated for total IBDQ score at each visit.
- (7) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in IBDQ total score at Week 10 from baseline (Week 0).

2.5 Statistical and Analytical Issues

2.5.1 Adjustments for Covariates

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	Clinical response at Week 10	[Clinical response, Non-response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
Adjustment factors:	Prior TNF α antagonist use	[Yes, No]
	Concomitant use of immunomodulators at Week 0	[Yes, No]
	Concomitant use of oral corticosteroids at Week 0	[Yes, No]
	Complete Mayo score at Week 0	[0 ≤ - ≤8, 9 ≤ - ≤12]
Analysis methodology:	Influences of the above adjustment factors on odds ratios for the clinical response at Week 10 and clinical remission at Week 10 will be investigated with the following analyses.	

By performing the CMH test using the above adjustment factors as

stratification factors and providing adjusted odds ratios of the MLN0002 group compared to the placebo group (MLN0002 group /placebo group) along with the 95% two-sided CI estimates, adjusted odds ratios for clinical response at Week 10 after adjusting influence of stratification factors will be investigated. In addition, interactions between treatment and adjustment factors will be investigated using the Breslow-Day test.

2.5.2 Handling of Dropouts or Missing Data

The efficacy endpoints of clinical response, clinical remission, or mucosal healing will be considered as non-response, non-remission, or non-healing, when adjudication for these endpoints is missing at the time of evaluation.

For other endpoints, missing data and ineligible data according to the “Handling Rules for Analysis Data” or the SAP will be excluded from statistical analyses and estimations.

Values below the limit of quantification will be handled as 0.

2.5.3 Interim Analyses and Data Monitoring

No interim analyses will be performed for the induction and maintenance phases.

In the open-label cohort, the data for the marketing application as fixed on the cut-off date will be analyzed after fixing the data of all subjects fixed on the cut-off date for the marketing application. Continuation/termination of the study, and change in clinical trial plan, and so on will not be judged based on the analysis.

2.5.4 Multicenter Studies

Although this is a multicenter study, interactions between treatment and study site will not be investigated since the target number of subjects per study site is not sufficiently large for meaningful analyses of the interactions.

2.5.5 Multiple Comparisons/Multiplicity

Since the study has different objectives in the induction and maintenance phases, no adjustments for multiplicity will be made between the analyses of the two phases setting the significance level at 5% each.

In the induction phase, the main focuses will be placed on the results of the CMH test in the primary analysis performed for the primary endpoint in the induction phase defined as clinical response at Week 10 and the results of CMH tests performed for clinical remission at Week 10, among the secondary endpoints in the induction phase in the “full analysis set in the induction phase.” In these analyses, the MLN0002 group will be compared with the placebo group based on closed testing procedures to maintain the overall type I error rate below 5% in the induction phase. Other analytical results will be interpreted to support the results of the primary endpoint or to explore the characteristics of efficacy of MLN0002. These results will be considered one measure suggesting the trends or characteristics of

efficacy. Thus, no adjustment for multiplicity will be performed.

2.5.6 Use of an “Efficacy Subset of Subjects”

To confirm the robustness of the primary analysis results for the primary endpoint for the sensitivity point of view, the same analysis as for the “full analysis set in the induction phase” will be performed secondarily in the “per protocol set in the induction phase.”

2.5.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority

Not applicable.

2.5.8 Examination of Subgroups

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	Clinical response at Week 10	[Clinical response, Non-response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
Stratum:	Age (years)	[Min≤ - ≤34, 35≤ - ≤Max] [Min≤ - ≤64, 65≤ - ≤Max]
	Gender	[Male, Female]
	Duration of UC (years)	[Min≤ - <7, 7≤ - ≤Max]
	Prior corticosteroids failure	[Yes, No]
	Prior immunomodulators failure	[Yes, No]
	Prior TNFα antagonist failure	[Yes, No]
	Number of drugs of TNFα antagonist failure	[1 drug, 2 drugs, 3 drugs, None]
	Classification of prior TNFα antagonist failure	[Inadequate response, Loss of response, Intolerance]
	Worst prior treatment failures	[Prior TNFα antagonist failure, Prior immunomodulators failure but not TNFα antagonist failure, Prior corticosteroid failure only]
	Prior immunomodulators and TNFα antagonist failure	[Yes, No]
	Concomitant use of immunomodulators at Week 0	[Yes, No]
	Concomitant use of oral corticosteroids at Week 0	[Yes, No]
	No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0	[Yes, No]

Concomitant use of oral corticosteroids and concomitant use of immunomodulators at Week 0 (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0	[Yes, No]
Complete Mayo score at Week 0	[0 ≤ - ≤ 8, 9 ≤ - ≤ 12]
Disease localization	[Total colitis, Left-sided colitis]
Weight (kg) at Week 0	[Min ≤ - ≤ 59.9, 60.0 ≤ - ≤ Max]

Analysis methodology: The following analysis will be performed for each of the above analysis variables by treatment group in the induction phase for each stratum. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy.

- (1) Frequency distributions will be provided along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.

3 SAFETY ANALYSIS

3.1 Treatment-Emergent Adverse Event

3.1.1 Overview of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set in the induction phase
Analysis variables:	TEAEs in the induction phase
Categories:	Causality [Related, Not related] Intensity [Mild, Moderate, Severe]
Analysis methodology:	The following summaries will be provided for the above analysis variables by each “cohort and treatment group in the induction phase.” The similar analysis will be performed in the combined MLN0002 group in the Cohort 1 and Cohort 2.

- (1) Overview of TEAEs in the induction phase
 - 1) All TEAEs in the induction phase (number of events, number and percentage of subjects)
 - 2) Causal relationship between all TEAEs in the induction phase and study drug (number of events, number and percentage of subjects)
 - 3) Intensity of all TEAEs in the induction phase (number of events, number and percentage of subjects)
 - 4) TEAEs in the induction phase leading to study drug discontinuation (number of events, number and percentage of subjects)
 - 5) Serious TEAEs in the induction phase (number of events, number and percentage of subjects)
 - 6) Causal relationship between serious TEAEs in the induction phase and study drug (number of events, number and percentage of subjects)
 - 7) Serious TEAEs in the induction phase leading to study drug discontinuation (number of events, number and percentage of subjects)
 - 8) TEAEs in the induction phase leading to death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below:

[Number of subjects]

- In the case of “summaries by causality”
A subject with occurrences of TEAE in the induction phase in both categories (i.e., Related and Not related) will be counted once in the Related category.
- In the case of “summaries by intensity”
A subject with multiple occurrences of TEAE in the induction phase will be counted once for the TEAE with the maximum

intensity.

- In the case of summaries other than the above

A subject with multiple occurrences of TEAE in the induction phase will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

3.1.2 Displays of Treatment-Emergent Adverse Events

Analysis set: Safety analysis set in the induction phase

Analysis variables: TEAEs in the induction phase

Infusion reactions in the induction phase

Categories: Intensity [Mild, Moderate, Severe]

Time of onset (day) [1 ≤ - ≤28, 29 ≤ - ≤56, 57 ≤ - ≤84, 85 ≤ - ≤Max]

Study drug administration in [1, 2, 3]
the induction phase (times)

Analysis methodology: The following summaries will be provided for the above analysis variables using frequency distributions by each “cohort and treatment group in the induction phase.” The similar analysis will be performed in the combined MLN0002 group in the Cohort 1 and Cohort 2.

TEAEs will be coded by use of MedDRA and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

- (1) All TEAEs in the induction phase by SOC and PT
- (2) All TEAEs in the induction phase by SOC
- (3) All TEAEs in the induction phase by PT
- (4) Drug-related TEAEs in the induction phase by SOC and PT
- (5) Intensity of all TEAEs in the induction phase by SOC and PT
- (6) Intensity of drug-related TEAEs in the induction phase by SOC and PT
- (7) TEAEs in the induction phase leading to study drug discontinuation by SOC and PT
- (8) Serious TEAEs in the induction phase by SOC and PT
- (9) Serious drug-related TEAEs in the induction phase by SOC and PT
- (10) All TEAEs in the induction phase by SOC and PT over time

- (11) Infusion reaction in the induction phase by SOC and PT
- (12) Infusion reaction in the induction phase by study drug administration in the induction phase (times) by SOC and PT
- (13) TEAEs in the induction phase whose date of onset is the day of the study drug administration or the following day by SOC and PT
- (14) TEAEs in the induction phase whose date of onset is the day of the study drug administration or the following day by study drug administration in the induction phase (times) by SOC and PT
- (15) TEAEs in the induction phase whose incidence summarized by PT is 3% or higher in either treatment group or cohort 2 by SOC and PT

The frequency distribution and incidence will be provided according to the rules below:

[Number of subjects]

- In the case of “summaries by SOC and PT, by SOC, and by PT”
A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages of TEAE in the induction phase will be based on the number of subjects in the safety analysis set in the induction phase.
- In the case of “summaries of intensity by SOC and PT”
A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages of TEAE in the induction phase will be based on the number of subjects in the safety analysis set in the induction phase.
- In the case of “summaries by SOC and PT over time”
A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE in the induction phase for each time interval, the number of subjects at risk (i.e., “subjects who either have an exposure in the study or have an occurrence of TEAE in the induction phase, during or after the corresponding time interval”) will be used as the denominator. The number of subjects whose

“onset of any one of the TEAEs in the induction phase is within the time interval” will be used as the numerator.

- In the case of “summaries of the study drug administration in the induction phase (times) by SOC and PT”

A subject with a TEAE that occurs in more than one time of study drug administration is counted for all the administrations (times) that the TEAE occurs. For each administration, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE in the induction phase for each administration (time) in the induction phase, the number of subjects at risk (i.e., “subjects who received the first, etc., study drug administration in the induction phase”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAEs in the induction phase is at the time of first, etc., administration in the induction phase” will be used as the numerator.

3.2 Pretreatment Event

3.2.1 Displays of Pretreatment Events

Analysis set:	All subjects who signed the informed consent form
Analysis variables:	PTE
Analysis methodology:	The following summaries will be provided for the above analysis variables using frequency distributions. PTEs will be coded by use of MedDRA and will be summarized based on the SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. (1) All PTEs by SOC and PT (2) Serious PTEs by SOC and PT PTE will be counted according to the rules below: [Number of subjects] A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

3.3 Clinical Laboratory Evaluations and Other Safety Endpoints

3.3.1 Clinical Laboratory Evaluations

3.3.1.1 Hematology and Blood Biochemistry

Analysis set:	Safety analysis set in the induction phase
Analysis variables:	Hematology

Red blood cells (RBC)	White blood cells (WBC)	Hemoglobin
Hematocrit	Platelets	
WBC differentials (neutrophils/leukocytes, eosinophils/leukocytes, basophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes)		

Blood biochemistry

Albumin	AST(GOT)	ALT(GPT)
ALP	Amylase	Glucose
Total bilirubin	Total protein	γ-GTP
Total cholesterol	Triglyceride	Creatinine
BUN	Uric acid	Potassium
Sodium	Calcium	Phosphorus
Magnesium	Chloride	

Inflammatory markers

C-reactive protein (CRP)

Categories: Adjudication results based on normal reference range [Below lower limit of normal range, Within the range of normal range, Over upper limit of normal range]

Categories in SAP Appendix 2 (1)

Visit: Weeks 0, 2, 6, 10, 14, and 16 weeks after the last dose of the study drug (other than inflammatory markers)
Weeks 0, 2, 6, 10, and 14 (inflammatory markers)

Analysis methodology: The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase.”
The subjects who received the study drug in the maintenance phase or open-label cohort will be excluded from the analysis at 16 weeks after the last dose.
Refer to Appendix 2 of this SAP for laboratory test items subject to this analysis, categories in the shift table, MAV Criteria, and definition of elevated liver enzyme.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration for each visit
- (2) Case plots
- (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each post-baseline visit
- (4) Shift tables showing categories of SAP Appendix 2 (1) at Week 0 and each post-baseline visit

- (5) Overall frequency distributions of MAV in the induction phase
- (6) Overall frequency distributions of elevated liver enzymes in the induction phase

3.3.1.2 Urinalysis

Analysis set:	Safety analysis set in the induction phase	
Analysis variables:	pH Urine specific gravity Glucose Protein Occult blood Bilirubin Ketone body	
Categories:	Adjudication results based on reference values	[Below lower limit of reference value, Within the range of reference value, Over upper limit of reference value]
Visit:	Weeks 0, 10, 14, and 16 weeks after the last dose of the study drug	
Analysis methodology:	<p>The following analyses of (1), (2), and (3) will be performed for pH and specific gravity by each “cohort and treatment group in the induction phase.” The following analysis of (3) will be performed for the above analysis variables other than pH and specific gravity by each “cohort and treatment group in the induction phase.”</p> <p>The subjects who received the study drug in the maintenance phase or open-label cohort will be excluded from the analysis at 16 weeks after the last dose.</p> <ul style="list-style-type: none"> (1) Summary statistics for each visit and summary statistics of differences before and after administration (2) Case plots (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each post-baseline visit 	

3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety

3.3.2.1 Vital Signs, Body Weight

Analysis set:	Safety analysis set in the induction phase
Analysis variables:	Systolic blood pressure Diastolic blood pressure Pulse Body temperature Weight
Visit:	Weeks 0, 2, 6, 10, 14, and 16 weeks after the last dose of the study

drug

Analysis methodology: The following analysis will be performed for the above analysis variables by each “cohort and treatment group in the induction phase.”

The subjects who received the study drug in the maintenance phase or open-label cohort will be excluded from the analysis at 16 weeks after the last dose.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration for each visit
- (2) Case plots

3.3.2.2 12-Lead ECG

Analysis set: Safety analysis set in the induction phase

Analysis variables: Findings of 12-lead ECG [Within normal limits, Abnormal but not clinically significant, Abnormal and clinically significant]

Visit: Weeks 0 and 10, and 16 weeks after the last dose of the study drug

Analysis methodology: The following analysis will be performed for the findings of 12-lead ECG by each “cohort and treatment group in the induction phase”

The subjects who received the study drug in the maintenance phase or open-label cohort will be excluded from the analysis at 16 weeks after the last dose.

- (1) Shift tables at Week 0 and each post-baseline visit

3.4 Display of Treatment-Emergent Adverse Event (in Japanese)

Analysis set: Safety analysis set in the induction phase

Analysis variables: TEAE in the induction phase (by SOC and PT)
Infusion reaction in the induction phase by SOC and PT

Analysis methodology: The similar summaries as 3.1.2 section will be provided for the above analysis variables. SOC and PT will be displayed in Japanese.

4 PHARMACOKINETIC ANALYSIS

4.1 Analysis of Serum Concentrations of MLN0002

Analysis set:	Subjects who underwent proper determination of serum concentrations of MLN0002 among the “full analysis set in the induction phase” and “subjects who were allocated in the Cohort 2 and received at least one dose of the study drug.”
Analysis variables:	Serum concentrations of MLN0002
Visit:	Weeks 2, 6, 10, and 14
Analysis methodology:	The following analysis will be performed for the above analysis variables by each cohort (MLN0002 group in Cohort 1 and Cohort 2) in the induction phase and in the consolidated cohorts in the induction phase. When calculating geometric mean and geometric CV%, the analysis will be performed by excluding the data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV% (2) Mean/standard deviation plot

4.2 Serum Concentrations of MLN0002 by Efficacy Endpoints

Analysis set:	Subjects who underwent proper determination of serum concentrations of MLN0002 among the “full analysis set in the induction phase” and “subjects who were allocated in the Cohort 2 and received at least one dose of the study drug.”
Analysis variables:	Serum concentrations of MLN0002
Stratum:	Clinical response at Week 10 [Clinical response, Non-response] Clinical remission at Week 10 [Clinical remission, Non-remission] Mucosal healing at Week 10 [Mucosal healing, Non-healing]
Visit:	Weeks 2, 6, 10, and 14
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by each cohort in the induction phase and in consolidated cohorts in the induction phase. When calculating geometric mean and geometric CV%, the analysis will be performed by excluding the data for which serum concentration of MLN0002 is 0. The adjudication results in the study site will be used as the score of findings on endoscopy. (1) Summary statistics, Geometric mean, and Geometric CV%

4.3 Serum Concentrations of MLN0002 by AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of serum concentrations of MLN0002 among the “full analysis set in the
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induction phase” and “subjects who were allocated in the Cohort 2 and received at least one dose of the study drug.”

Analysis variables: Serum concentrations of MLN0002

Stratum: AVA at Week 10 [Negative, Positive]
Neutralizing antibody at Week 10 [Negative, Positive]

Visit: Weeks 2, 6, 10, and 14

Analysis methodology: The following analysis will be performed for the above analysis variables for each stratum by each cohort in the induction phase and in consolidated cohorts in the induction phase. When calculating geometric mean and geometric CV%, the analysis will be performed by excluding the data for which serum concentration of MLN0002 is 0.

(1) Summary statistics, geometric mean, and geometric CV%

4.4 Efficacy by Serum Concentration of MLN0002

Analysis set: Subjects who underwent proper determination of serum concentrations of MLN0002 among the “full analysis set in the induction phase” and “subjects who were allocated in the Cohort 2 and received at least one dose of the study drug.”

Analysis variables: Clinical response at Week 10 [Clinical response, Non-response]
Clinical remission at Week 10 [Clinical remission, Non-remission]
Mucosal healing at Week 10 [Mucosal healing, Non-healing]

Stratum: Serum concentrations of MLN0002 at Week 2 [0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]
Serum concentrations of MLN0002 at Week 6 [0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]
Serum concentrations of MLN0002 at Week 10 [0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]

Visit: Week 10

Analysis methodology: The following analysis will be performed for the above analysis variables for each stratum by each cohort in the induction phase and in consolidated cohorts in the induction phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy. Categories of stratum will be defined as 4 categories with the first quartile (Q1), median, and third quartile

(Q3) of the obtained data as boundaries.

(1) Frequency distributions, point estimates and 95% two-sided CI for the proportion

5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS

5.1 AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody among the “full analysis set in the induction phase” and “subjects who received at least one dose of the study drug in the Cohort 2”	
Analysis variables:	AVA	[Negative, Positive]
	AVA titer	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Neutralizing antibody	[Negative, Positive]
Visit:	Weeks 0 and 10, and 16 weeks after the last dose of the study drug	
Analysis methodology:	The following analysis will be performed for the above analysis variables by each cohort in the induction phase and in consolidated cohorts in the induction phase. The category of AVA titer will be set according to the observed AVA titer. The subjects who received the study drug in the maintenance phase or open-label cohort will be excluded from the analysis at 16 weeks after the last dose. (1) Frequency distributions	

5.2 Efficacy by AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody among the “full analysis set in the induction phase” and “subjects who received at least one dose of the study drug in the Cohort 2”	
Analysis variables:	Clinical response at Week 10	[Clinical response, Non-response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
	Mucosal healing at Week 10	[Mucosal healing, Non-healing]
Stratum:	AVA at Week 10	[Negative, Positive]
	Neutralizing antibody at Week 10	[Negative, Positive]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by each cohort in the induction phase and in consolidated cohorts in the induction phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy. (1) Frequency distributions	

5.3 AVA and Neutralizing Antibody by Concomitant Use of Immunomodulators

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody among the “full analysis set in the induction phase” and “subjects who received at least one dose of the study drug in the Cohort 2”
Analysis variables:	AVA [Negative, Positive] Neutralizing antibody [Negative, Positive]
Stratum:	Concomitant use of immunomodulators at Week 0 [Yes, No] No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only) [Yes, No] Concomitant use of oral corticosteroids at Week 0 [Yes, No]
Visit:	Weeks 0 and 10, and 16 weeks after the last dose of the study drug
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by each cohort in the induction phase and in consolidated cohorts in the induction phase. The subjects who received the study drug in the maintenance phase or open-label cohort will be excluded from the analysis at 16 weeks after the last dose. (1) Frequency distributions

6 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT

- Significance level: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided estimate)

History of Revision (version management)

Version	Date	Prepared/modified by	Comments
First version	24 February 2017	PPD	Preparation of first version

[Appendix 1] Comparison Table for Changes

N/A

[Appendix 2] Definitions of Categories in Shift Table, MAV Criteria, and Criteria for Elevated Liver Enzyme

(1) Categories in Shift Table

The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

Test item	Categories
Albumin	\geq LLN, <LLN to 3 g/dL, <3 g/dL to 2 g/dL, <2 g/dL to 1 g/dL, <1 g/dL
ALT(GPT)	\leq ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
AST(GOT)	\leq ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
Total bilirubin	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 3.0×ULN, >3.0×ULN to 10.0×ULN, >10.0×ULN
Creatinine	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 3.0×ULN, >3.0×ULN to 6.0×ULN, >6.0×ULN
ALP	\leq ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
WBC	\geq LLN, <LLN to 3000/ μ L, <3000/ μ L to 2000/ μ L, <2000/ μ L to 1000/ μ L, <1000/ μ L
WBC	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Platelets	\geq LLN, <LLN to 7.5×10 ⁴ / μ L, <7.5×10 ⁴ / μ L to 5.0×10 ⁴ / μ L, <5.0×10 ⁴ / μ L to 2.5×10 ⁴ / μ L, <2.5×10 ⁴ / μ L
Platelets	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN to 3.0×ULN, >3.0×ULN
Lymphocytes	\geq 800/ μ L, <800/ μ L to 500/ μ L, <500/ μ L to 200/ μ L, <200/ μ L
Lymphocytes (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Eosinophils (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Monocytes (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Basophils (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Hemoglobin	\geq LLN, <LLN to 10 g/dL, <10 g/dL to 8 g/dL, <8 g/dL to 6.5 g/dL, <6.5 g/dL
Neutrophils	\geq 1500/ μ L, <1500/ μ L to 1000/ μ L, <1000/ μ L to 500/ μ L, <500/ μ L
Neutrophils (%)	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN to 3.0×ULN, >3.0×ULN

Missing data will not be included in any category.

(2) MAV Criteria

1) Hematology, Blood Biochemistry

For each test item, MAV will be determined according to the table below for evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) obtained from the day after the first dose of the study drug in the induction phase until the day of the first dose of the study drug in the maintenance phase or open-label cohort for subjects who received the study drug in the maintenance phase or open-label cohort or from the day after the first dose of the study drug in the induction phase until 167 days* after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the maintenance phase and open-label cohort. The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

* Day after the last dose of the study drug will be defined as Follow-up Day 1.

Test item	MAV Criteria	
	Lower criteria	Upper criteria
Hemoglobin (g/dL)	≤7	-
Lymphocytes (/μL)	<500	-
WBC (/μL)	<2000	-
Platelets (×10 ⁴ /μL)	<7.5	-
Neutrophils (/μL)	<1000	-
ALT(GPT) (U/L)	-	>3.0×ULN
AST(GOT) (U/L)	-	>3.0×ULN
Total bilirubin (mg/dL)	-	>2.0×ULN
Amylase (U/L)	-	>2.0×ULN

Classifying Subjects for the Overall Induction Phase

For each test item and subject, MAV will be determined according to the conditions [1] to [3] provided below.

- [1] A subject will be classified as those “with MAV” if he/she has at least one data that “meets the MAV Criteria” among the evaluable data obtained from the day after the first dose of the study drug in the induction phase until the day of the first dose of the study drug in the maintenance phase or open-label cohort for subjects who received the study drug in the maintenance phase or open-label cohort or from the day after the first dose of the study drug in the induction phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the maintenance phase and open-label cohort.
- [2] A subject will be classified as those “without MAV” if he/she does not meet condition [1] and has at least one data that does “not meet the MAV Criteria” among the evaluable data obtained from the day after the first dose of the study drug in the induction phase until the day of the first dose of the study drug in the maintenance phase or open-label cohort for subjects who received the study drug in the maintenance phase or open-label cohort or from the day after the first dose of the study drug in the induction phase until 167 days after the last dose of the study drug

(including Follow-up Day 167) for subjects who did not receive the study drug in the maintenance phase and open-label cohort.

- [3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of MAV for that item.

(3) Criteria for Elevated Liver Enzyme

For each test item, elevated liver enzyme will be determined according to the table below for evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) obtained from the day after the first dose of the study drug in the induction phase until the day of the first dose of the study drug in the maintenance phase or open-label cohort for subjects who received the study drug in the maintenance phase or open-label cohort or from the day after the first dose of the study drug in the induction phase until 167 days* after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the maintenance phase and open-label cohort. If there is more than one item that need to be considered for a criteria, test items measured on the same day will be used. The following abbreviations are used in the table below: LLN for lower limit of the normal range, ULN for upper limit of the normal range, ALT for alanine aminotransferase, AST for aspartate aminotransferase, Tbili for total bilirubin, and ALP for alkaline phosphatase.

* Day after the last dose of the study drug will be defined as Follow-up Day 1.

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
ALT > 3×ULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5×ULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8×ULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3×ULN with Tbili > 2×ULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3×ULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5×ULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8×ULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN
AST > 3×ULN with Tbili > 2×ULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3×ULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5×ULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
ALT or AST > 8×ULN	Either ALT or AST is greater than 8 times the ULN	Both ALT and AST are non-missing and less than or equal to 8 times the ULN
ALT or AST > 3×ULN with Tbili > 2×ULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN. - Total bilirubin is non-missing and less than or equal to twice the ULN.
ALT and AST > 3×ULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN
ALT and AST > 5×ULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8×ULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3×ULN with Tbili > 2×ULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3×ULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3×ULN with ALT > 3×ULN	Both ALP and ALT are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3×ULN with AST > 3×ULN	Both ALP and AST are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

Classifying Subjects for the Overall Induction Phase

For each criteria and subject, “elevated liver enzyme” will be determined according to the conditions [1] to [3] provided below.

- [1] A subject will be classified as those “with elevated liver enzyme” if he/she has at least one data that “meets the criteria for elevated liver enzyme” among the evaluable data obtained from the day after the first dose of the study drug in the induction phase until the day of the first dose of the study drug in the maintenance phase or open-label cohort for subjects who received the study drug in the maintenance phase or open-label cohort or from the day after the first dose of the study drug in the induction phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the maintenance phase and open-label cohort.
- [2] A subject will be classified as those “without elevated liver enzyme” if he/she does not meet condition [1] and has at least one data that does “not meet the criteria for elevated liver enzyme” among the evaluable data obtained from the day after the first dose of the study drug in the induction phase until the day of the first dose of the study drug in the maintenance phase or open-label cohort for subjects who received the study drug in the maintenance phase or open-label cohort or from the day after the first dose of the study drug in the induction phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the maintenance phase and open-label cohort.
- [3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of elevated liver enzyme for that item.

STATISTICAL ANALYSIS PLAN (Maintenance Phase)

Study Title : Phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and pharmacokinetics of intravenous MLN0002 (300 mg) infusion in induction and maintenance therapy in Japanese subjects with moderate or severe ulcerative colitis

Protocol No. : MLN0002/CCT-101

Sponsor : Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

PPD [Redacted] Takeda Pharmaceutical Company Limited

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Trial Statistician

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Limited

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 3

HANDLING OF TIME WINDOW 4

OTHER HANDLING 10

1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS 22

1.1 Disposition of Subjects 22

 1.1.1 Study Information 22

 1.1.2 Disposition of All Subjects Who Did Not Enter in the Maintenance Phase 22

 1.1.3 Subject Eligibility 22

 1.1.4 Number of Subjects Who Entered in the Maintenance Phase by Site..... 22

 1.1.5 Disposition of Subjects 23

 1.1.5.1 Disposition of Subjects 23

 1.1.6 Study Drug Completion Status and Study Visit Completion Status 24

 1.1.7 Protocol Deviations and Analysis Sets 25

1.2 Demographic and Other Baseline Characteristics..... 27

 1.2.1 Distribution of Baseline Demographics..... 27

 1.2.2 Medical History, Concurrent Medical Conditions..... 29

 1.2.3 Medication History, Concomitant Medications in the Maintenance Phase, Concomitant Therapies in the Maintenance Phase 30

1.3 Measurement of Compliance Status for Treatment 32

 1.3.1 Study Drug Exposure and Compliance in the Maintenance Phase 32

2 EFFICACY ANALYSIS 34

2.1 Primary Endpoints and Analysis Methodology 34

 2.1.1 Primary Analysis..... 34

 2.1.2 Secondary Analysis..... 34

2.2 Secondary Endpoints and Analysis Methodology 35

2.3 Other Endpoints and Analysis Methodology 37

 2.3.1 Endpoints Related to Mayo Scores 37

 2.3.2 Endpoints Related to IBDQ 40

 2.3.3 Endpoints Related to Oral Corticosteroid Dosage 43

 2.3.4 Endpoints Related to Time to Onset of Event..... 43

2.4 Analysis of Subjects in the Placebo Continuation Group 44

2.5 Statistical and Analytical Issues..... 45

 2.5.1 Adjustments for Covariates..... 45

 2.5.2 Handling of Dropouts or Missing Data..... 46

 2.5.3 Interim Analyses and Data Monitoring..... 46

 2.5.4 Multicenter Studies 46

2.5.5 Multiple Comparisons/Multiplicity.....	47
2.5.6 Use of an “Efficacy Subset of Subjects”.....	47
2.5.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority	47
2.5.8 Examination of Subgroups.....	47
3 SAFETY ANALYSIS.....	50
3.1 Treatment-Emergent Adverse Event.....	50
3.1.1 Overview of Treatment-Emergent Adverse Events	50
3.1.2 Displays of Treatment-Emergent Adverse Events.....	51
3.2 Pretreatment Event.....	53
3.2.1 Displays of Pretreatment Events.....	53
3.3 Clinical Laboratory Evaluations and Other Safety Endpoints	53
3.3.1 Clinical Laboratory Evaluations	53
3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety	55
3.4 Display of Treatment-Emergent Adverse Event (in Japanese).....	56
4 PHARMACOKINETIC ANALYSIS	57
4.1 Analysis of Serum Concentrations of MLN0002.....	57
4.2 Serum Concentrations of MLN0002 by Efficacy Endpoints	57
4.3 Serum Concentrations of MLN0002 by AVA and Neutralizing Antibody.....	57
4.4 Efficacy by Serum Concentration of MLN0002.....	58
5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS.....	60
5.1 AVA and Neutralizing Antibody	60
5.2 Efficacy by AVA and Neutralizing Antibody.....	60
5.3 AVA and Neutralizing Antibody by Concomitant Use of Immunomodulators.....	60
6 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT	62
History of Revision (version management)	63
[Appendix 1] Comparison Table for Changes	1
[Appendix 2] Definitions of Categories in Shift Table, MAV Criteria, and Criteria for Elevated Liver Enzyme	1

Since the study has different objectives in the induction phase, the maintenance phase and the open-label cohort, analyses will be conducted separately among these. Therefore, the “Statistical Analysis Plan” will be also prepared for the induction phase, maintenance phase, and open-label cohort respectively. This statistical analysis plan will describe the analytical plan in the maintenance phase.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

- Treatment-emergent adverse event (TEAE) in the maintenance phase: An adverse event that emerged during the maintenance phase.
- All subjects entered in the maintenance phase: Of subjects who achieved clinical response at Week 10, those who were enrolled into the maintenance phase.
- Concomitant medication in the maintenance phase: Any concomitant medication which was started by the day before the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort. “By the day before the first dose of the study drug in the open-label cohort” will include the day before the first dose of the study drug in the open-label cohort. Hereinafter, the same expression (by -) will be interpreted in the same manner. For subjects who did not receive the study drug in the open-label cohort, all concomitant medications are included.
- Concomitant therapy in the maintenance phase: Any concomitant therapy which was started by the day before the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort. For subjects who did not receive the study drug in the open-label cohort, all concomitant therapies are included.
- Summary statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- MAV: An abbreviation for markedly abnormal value.
- Study Day: The day before the first dose of the study drug in the induction phase will be defined as Day -1 and the day of the first dose in the induction phase will be defined as Day 1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1. There will be no distinction among the induction phase, maintenance phase, and open-label cohort for the day of the last dose of the study drug.
- Full analysis set in the maintenance phase: Subjects who were randomized and received at least one dose of the study drug in the maintenance phase. The full analysis set in the maintenance phase will not include subjects who received placebo in the induction phase and were enrolled into the maintenance phase.
- Per protocol set in the maintenance phase: All subjects in full analysis set in the maintenance phase who did not have any major protocol deviations, have met the minimum protocol

provisions, and have evaluable primary endpoint(s).

- Safety analysis set in the maintenance phase: Subjects who received at least one dose of the study drug in the maintenance phase.
- Treatment groups in the maintenance phase: MLN0002 group and placebo group.
- Anti-vedolizumab antibody (AVA): Human anti-human antibody (HAHA) in the protocol will be described as AVA.
- Subjects in the placebo continuation group: Subjects who were allocated to the placebo group in the induction phase and received the placebo in the maintenance phase.
- Treatment groups in the maintenance phase and subjects in the placebo continuation group: MLN0002 group, placebo group, and subjects in the placebo continuation group.
- Responders at Week 10: Subjects who were determined to have achieved clinical response at Week 10 on the website of the registration center.
- Responders at Week 10 who received MLN0002 in the induction phase: Responders at Week 10 in the MLN0002 group of the full analysis set in the induction phase or responders at Week 10 in the Cohort 2 in the induction phase.
- Cohorts and treatment groups in the induction phase: MLN0002 group in the induction phase, placebo group in the induction phase, and Cohort 2.

HANDLING OF TIME WINDOW

For each test, observation, and evaluation item, evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) will be handled according to the following rules.

For acceptable windows of evaluation items other than oral corticosteroid dosage at each visit except for Week 0, the evaluable data within the acceptable window for subjects who received the study drug in the maintenance phase or open-label cohort will be used among the data measured prior to the day of the first dose of the study drug in the open-label cohort. The evaluable data within the acceptable window will be used for other subjects. If more than one datum lies within the same acceptable window, the data whose test/observation/evaluation date is closest to the scheduled date will be used and, if there are two data equidistant to the scheduled date, the data obtained later will be used. The temporal distance from the scheduled date will be determined based on the Study Day and Follow-up Day.

Oral corticosteroid dosage is described in “OTHER HANDLING.”

If the date of the first dose of the study drug in the open-label cohort is smaller than the lower limit of the acceptable window in the table, the acceptable window at that visit will not be applied.

Complete Mayo score*¹, Mayo subscore (findings on endoscopy)*²

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	
Week 60	Study Day: 421	393 to 448	

*¹ Clinical response and clinical remission will be determined based on complete Mayo scores.

*² Mucosal healing will be determined based on Mayo subscores (findings on endoscopy).

Partial Mayo score*¹, Mayo subscore (stool frequency, rectal bleeding, physician's global assessment)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 2	Study Day: 15	2 to 28	
Week 6	Study Day: 43	29 to 56	
Week 10	Study Day: 71	57 to 84	
Week 14	Study Day: 99	85 to 112	
Week 18	Study Day: 127	113 to 140	
Week 22	Study Day: 155	141 to 168	
Week 26	Study Day: 183	169 to 196	
Week 30	Study Day: 211	197 to 224	
Week 34	Study Day: 239	225 to 252	
Week 38	Study Day: 267	253 to 280	
Week 42	Study Day: 295	281 to 308	
Week 46	Study Day: 323	309 to 336	
Week 50	Study Day: 351	337 to 364	
Week 54	Study Day: 379	365 to 392	
Week 58	Study Day: 407	393 to 413	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 60	Study Day: 421	414 to 448	
Week 60 (LOCF)* ²			

*¹ Clinical response based on partial Mayo score will be determined based on partial Mayo scores.

*² For Week 60 (LOCF), the latest data during the period from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort will be used for subjects who received the study drug in the open-label cohort. For subjects who did not receive the study drug in the open-label cohort, the latest data during the period from the day after the first dose of the study drug in the maintenance phase onwards will be used.

IBDQ scores (total score and each subscore [abdominal symptoms, general condition, emotion, and social function])

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	
Week 14	Study Day: 99	85 to 182	
Week 38	Study Day: 267	183 to 343	
Week 60	Study Day: 421	344 to 448	
Week 60 (LOCF)* ¹			

*¹ For Week 60 (LOCF), the latest data during the period from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort will be used for subjects who received the study drug in the open-label cohort. For subjects who did not receive the study drug in the open-label cohort, the latest data during the period from the day after the first dose of the study drug in the maintenance phase onwards will be used.

Laboratory tests (hematology, blood biochemistry, inflammatory markers)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 2	Study Day: 15	2 to 28	
Week 6	Study Day: 43	29 to 56	
Week 10	Study Day: 71	57 to 84	
Week 14	Study Day: 99	85 to 126	
Week 22	Study Day: 155	127 to 182	
Week 30	Study Day: 211	183 to 238	
Week 38	Study Day: 267	239 to 294	
Week 46	Study Day: 323	295 to 350	
Week 54	Study Day: 379	351 to 399	
Week 60	Study Day: 421	400 to 448	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the open-label cohort. Not applied to laboratory test (inflammatory markers).

Laboratory test (urinalysis)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	
Week 14	Study Day: 99	85 to 126	
Week 60	Study Day: 421	127 to 448	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the open-label cohort.

Vital signs, body weight

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 2	Study Day: 15	2 to 28	
Week 6	Study Day: 43	29 to 56	
Week 10	Study Day: 71	57 to 84	
Week 14	Study Day: 99	85 to 112	
Week 18	Study Day: 127	113 to 140	
Week 22	Study Day: 155	141 to 168	
Week 26	Study Day: 183	169 to 196	
Week 30	Study Day: 211	197 to 224	
Week 34	Study Day: 239	225 to 252	
Week 38	Study Day: 267	253 to 280	
Week 42	Study Day: 295	281 to 308	
Week 46	Study Day: 323	309 to 336	
Week 50	Study Day: 351	337 to 364	
Week 54	Study Day: 379	365 to 392	
Week 58	Study Day: 407	393 to 413	
Week 60	Study Day: 421	414 to 448	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the open-label cohort.

12-lead ECG

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 60	Study Day: 421	85 to 448	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the open-label cohort.

AVA, neutralizing antibody

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	-28 to 1	
Week 10	Study Day: 71	2 to 84	
Week 30	Study Day: 211	85 to 315	
Week 60	Study Day: 421	316 to 448	
16 weeks after the last dose* ¹	Follow-up Day: 112		56 to 167

*¹ Applied only to subjects who did not receive the study drug in the open-label cohort.

Serum concentrations of MLN0002

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 2* ¹	Study Day: 15	12 to 18	
Week 6* ¹	Study Day: 43	40 to 46	
Week 10	Study Day: 71	68 to 74	
Week 14* ¹	Study Day: 99	92 to 106	
Week 22* ¹	Study Day: 155	148 to 162	
Week 30* ¹	Study Day: 211	204 to 218	
Week 60	Study Day: 421	314 to 428	

*¹ For Weeks 2, 6, 14, 22, and 30, only data measured from 3 hours before administration until immediately before administration will be used.

OTHER HANDLING

In principle, if any variable value used for calculation or adjudication is missing, the result of the calculation or adjudication will be handled as missing. If other handling of missing data is described, follow that handling.

- Duration of study drug exposure in the maintenance phase (day): Date of the last dose of the study drug in the maintenance phase – Date of the first dose of the study drug in the maintenance phase + 1
- Duration on study after the first dose of the study drug in the maintenance phase (day): For subjects who received the study drug in the open-label cohort, “date of the first dose of the study drug in the open-label cohort – Date of the first dose of the study drug in the maintenance phase” and for other subjects, “date of last visit or contact – date of the first dose of the study drug in the maintenance phase + 1”
- $BMI (kg/m^2) = Weight (kg) / (Height [cm]/100)^2$ (round off to the first decimal place)
- Duration of UC (year): (Date of informed consent [year and month] – Date of UC diagnosis [year and month]) / 12 (round off to the first decimal place)
 - Only year and month for date of informed consent will be used.
 - The unit for “Date of informed consent (year and month) – Date of UC diagnosis (year and month)” will be “months.”
 - If the year of UC diagnosis is unknown, the duration of UC will be handled as “Missing.” If only the month of UC diagnosis is unknown, the duration of UC will be calculated by setting the month of UC diagnosis as January.
- Prior corticosteroids failure: If corticosteroids resistance, dependence, or intolerance is “Yes,” prior corticosteroids failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Classification 1 of prior corticosteroids failure: Subjects for whom prior corticosteroid failure is “Yes” are classified as follows:
 - Subjects for whom corticosteroid resistance is “Yes” are classified as “Resistance.”
 - Among subjects for whom corticosteroids resistance is not “Yes,” subjects for whom corticosteroid dependence is “Yes” are classified as “Dependence.”
 - Among subjects for whom corticosteroids resistance is not “Yes” as well as corticosteroid dependence not being “Yes,” subjects for whom corticosteroid intolerance is “Yes” are classified as “Intolerance.”
- Classification 2 of prior corticosteroids failure: Subjects for whom prior corticosteroid failure is “Yes” are classified as follows:
 - Subjects for whom corticosteroid resistance is “Yes” or corticosteroid dependence is “Yes” are classified as “Refractory.”

- Among subjects for whom corticosteroids resistance is not “Yes” as well as corticosteroid dependence not being “Yes,” subjects for whom corticosteroid intolerance is “Yes” are classified as “Intolerance.”
- Prior immunomodulators failure: If either of immunomodulator refractory or intolerance is “Yes,” prior immunomodulators failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Classification of prior immunomodulators failure: Subjects for whom prior immunomodulators failure is “Yes” are classified as follows:
 - Subjects for whom immunomodulator refractory is “Yes” are classified as “Refractory.”
 - Among the subjects for whom immunomodulator refractory are not “Yes,” subjects for whom immunomodulatory intolerance is “Yes” are classified as “Intolerance.”
- Prior TNF α antagonist failure: If inadequate response, loss of response, or intolerance to the TNF α antagonist is “Yes,” prior TNF α antagonist failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Number of drugs of TNF α antagonist failure: Among the drugs entered to prior treatment failure (TNF α antagonist) for UC, subjects whose Who Drug is coded with 1 type of drug with Preferred Name are classified as “Treatment failure with 1 drug.” Similarly, subjects who are coded with 2 types of drugs are classified as “Treatment failure with 2 drugs” and subjects who are coded with 3 types of drugs as “Treatment failure with 3 drugs.” Subjects who are not coded with any drug in the prior treatment failure (TNF α antagonist) for UC are classified as “None.”
- Classification of prior TNF α antagonist failure: Subjects for whom TNF α antagonist failure is “Yes” are classified as follows:
 - Subjects for whom TNF α antagonist inadequate response is “Yes” are classified as “Inadequate response.”
 - Among subjects for whom TNF α antagonist inadequate response is not “Yes,” subjects for whom TNF α antagonist loss of response is “Yes” are classified as “Loss of response.”
 - Among subjects for whom TNF α antagonist inadequate response is not “Yes” as well as TNF α antagonist loss of response not being “Yes,” subjects for whom TNF α antagonist intolerance is “Yes” are classified as “Intolerance.”
- Prior immunomodulators failure (excluding prior TNF α antagonist failure): If prior TNF α antagonist failure is “No” and prior immunomodulators failure is “Yes,” prior immunomodulators failure (excluding prior TNF α antagonist failure) will be defined as “Yes.” All others will be defined as “No.”
- Prior corticosteroid failure only: If prior TNF α antagonist failure is “No,” prior immunomodulators failure is “No,” and prior corticosteroids failure is “Yes,” prior corticosteroid failure only will be defined as “Yes.” All others will be defined as “No.”
- Prior immunomodulators and TNF α antagonist failure: If prior immunomodulators failure is

“Yes” and prior TNF α antagonist failure is “Yes,” prior immunomodulators and TNF α antagonist failure will be defined as “Yes.” All others will be defined as “No.”

- Completion of the study drug infusion: If the infusion of the study drug is “Completed” or dose of the study drug is ≥ 79 mL (percentage of dose against prepared study drug of 105 mL is $\geq 75\%$), the study drug infusion will be defined as “Completed.” All others will be defined as “Incompleted.”

Mayo score will be handled as follows:

- Complete Mayo score: Sum of each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy, and physician’s global assessment).
 - The complete Mayo score will be calculated using subscores on the same day of measurement. The day of evaluation for stool frequency and rectal bleeding will be the same as the day of evaluation for physician’s global assessment.
 - If any Mayo subscore is missing, the complete Mayo score will be handled as missing.
- Clinical response: If the following 2 conditions are fulfilled, subjects will be classified as “Clinical response.” All others will be classified as “Non-response.” However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing “HANDLING OF TIME WINDOW,” subjects will be classified as “Non-response.”
 - Decrease of the complete Mayo score by ≥ 3 points and by $\geq 30\%$ from baseline (Week 0)
 - Decrease of the subscore of rectal bleeding by ≥ 1 point from baseline (Week 0) or ≤ 1 in the subscore of rectal bleeding
- Clinical remission: If the complete Mayo score is ≤ 2 and all subscores are ≤ 1 , subjects will be classified as “Clinical remission.” All others will be classified as “Non-remission.” However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing “HANDLING OF TIME WINDOW,” subjects will be classified as “Non-remission.”
- Mucosal healing: If the subscore for the findings on endoscopy is ≤ 1 , subjects will be classified as “Mucosal healing.” All others will be classified as “Non-healing.” However, if any of the scores used for adjudication are missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing “HANDLING OF TIME WINDOW,” subjects will be classified as “Non-healing.”
- 0 in the subscore for the findings on endoscopy: “Yes” if the subscore for the findings on endoscopy is 0 and “No” if it is ≥ 1 or missing.
- Partial Mayo score: Sum of subscores for stool frequency, rectal bleeding, and physician’s global assessment.

- The partial Mayo score will be calculated using subscores on the same day of measurement. The day of evaluation for stool frequency and rectal bleeding will be the same as the day of evaluation for physician's global assessment.
- If any of the subscores for stool frequency, rectal bleeding, and physician's global assessment used for calculation of the partial Mayo score are missing, the partial Mayo score will be handled as missing.
- Clinical response based on partial Mayo score: If the following 2 conditions are fulfilled, subjects will be classified as "Clinical response based on partial Mayo score." All others will be classified as "Non-response based on partial Mayo score." However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing "HANDLING OF TIME WINDOW," subjects will be classified as "Non-response based on partial Mayo score."
 - Decrease of the partial Mayo score by ≥ 2 points and by $\geq 25\%$ from baseline (Week 0)
 - Decrease of the subscore of rectal bleeding by ≥ 1 point from baseline (Week 0) or ≤ 1 in the subscore of rectal bleeding
- Durable response: If "Clinical response" is observed both at Week 10 and Week 60, subjects will be classified as "Durable response." All others will be classified as "Non-durable response."
 - At Weeks 10 and 60, the visit after processing "HANDLING OF TIME WINDOW" will be used.
- Durable remission: If "Clinical remission" is observed both at Week 10 and Week 60, subjects will be classified as "Durable remission." All others will be classified as "Non-durable remission."
 - At Weeks 10 and 60, the visit after processing "HANDLING OF TIME WINDOW" will be used.
- Disease worsening: All partial Mayo scores at visits including unscheduled ones during the period from the day after the first dose of the study drug in the maintenance phase until the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort, and all partial Mayo scores at visits including unscheduled ones during the period from the day after the first dose of the study drug in the maintenance phase onwards for subjects who did not receive the study drug in the open-label cohort will be handled as follows:
 - For subjects whose partial Mayo score at Week 10 is ≥ 7 points, if the partial Mayo scores become 9 points in 2 successive visits with ≥ 7 day interval (interval between visits shall not be less than 1 week) by confirming partial Mayo scores in ascending order of visit date, subjects will be classified as "Yes" for disease worsening. The onset date of disease

worsening will be defined as the earlier date among these 2 visits, after excluding missing values.

- For subjects whose partial Mayo score at Week 10 is ≤ 6 points, if the partial Mayo scores increase by ≥ 3 points from that of Week 10 and become ≥ 5 points in 2 successive visits with ≥ 7 day interval (interval between visits shall not be less than 1 week) by confirming partial Mayo scores in ascending order of visit date, subjects will be classified as “Yes” for disease worsening. The onset date of disease worsening will be defined as the earlier date among these 2 visits, after excluding missing values.
- Time to disease worsening: A subject for whom disease worsening was determined to be “Yes” will be handled as an event case, and the period of “Onset date of disease worsening – Date of the first dose of the study drug in the maintenance phase + 1” will be used for analysis. A subject for whom disease worsening was not determined to be “Yes” will be handled as a censored case, and the period of “date of the last measurement of partial Mayo score – date of first dose of the study drug in the maintenance phase + 1” will be used for analysis.
- Rescue treatments: All concomitant medications (for treatment of UC) or therapies that started during the period from the day of the first dose of the study drug in the maintenance phase until the day before the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort, and all concomitant medications (for treatment of UC) or therapies that started during the period from the day of the first dose of the study drug in the maintenance phase onwards for subjects who did not receive the study drug in the open-label cohort will be handled as follows:
 - Subjects with at least one concomitant medication or therapy that falls under the category of rescue treatment are classified as “Yes” for rescue treatments, and the start date of rescue treatment will be defined as the earliest date among the started dates of the concomitant rescue medications or therapies, after excluding missing values.
- Discontinuation due to study drug-related adverse event: The study drug completion status in the maintenance phase will be handled as follows:
 - Subjects who discontinued the study drug due to “Pretreatment event/Adverse event” are classified as “Yes” for discontinuation due to study drug-related adverse event, and the onset date of discontinuation due to study drug-related adverse event will be defined as the date of the study drug discontinuation.
- Time to treatment failure
 - If any of the study discontinuation due to disease worsening, rescue treatments, or study drug-related adverse event is “Yes,” treatment failure will be defined as “Yes,” and the onset date of the treatment failure will be defined as the earliest date among the onset dates of the study discontinuations, after excluding missing values.

- Time to treatment failure:
 - ✧ A subject for whom treatment failure was determined to be “Yes” will be treated as an event case, and time to treatment failure will be defined as the period of “Onset date of treatment failure – Date of the first dose of the study drug in the maintenance phase + 1.”
 - ✧ A subject for whom treatment failure was not determined to be “Yes” will be treated as a censored case.
 - ✧ For censored subjects who received the study drug in the open-label cohort, the period of “previous date of the first dose of the study drug in the open-label cohort – date of the first dose of the study drug in the maintenance phase + 1” will be used for analysis.
 - ✧ For censored subjects who did not receive the study drug in the open-label cohort, the period of “Date of last visit or contact in the maintenance phase – Date of the first dose of the study drug in the maintenance phase + 1” will be used for analysis.

- Time to major UC-related events (UC-related hospitalization, enterectomy)
 - Onset date of major UC-related events: The onset date of major UC-related events will be defined as the earliest date of UC-related hospitalization or enterectomy during the period from the day of the first dose of the study drug in the maintenance phase onwards, after excluding missing values. However, for subjects who received the study drug in the open-label cohort, if the date of the first dose of the study drug in the open-label cohort is earlier than the onset date of major UC-related events, the onset date of major UC-related events will be handled as missing.
 - Major UC-related events (UC-related hospitalization, enterectomy): If the onset date of major UC-related events is non-missing, major UC-related events (UC-related hospitalization, enterectomy) will be defined as “Yes.”
 - Time to major UC-related events (UC-related hospitalization, enterectomy):
 - ✧ A subject for whom major UC-related events was determined to be “Yes” will be treated as an event case, and time to major UC-related events will be defined as the period of “Onset date of major UC-related events – Date of the first dose of the study drug in the maintenance phase + 1.”
 - ✧ A subject for whom treatment failure was not determined to be “Yes” will be treated as a censored case.
 - ✧ For censored subjects who received the study drug in the open-label cohort, time to major UC-related events will be defined as the period of “Previous date of the first dose of the study drug in the open-label cohort – Date of the first dose of the study drug in the maintenance phase + 1.”

- ✧ For censored subjects who did not receive the study drug in the open-label cohort, time to major UC-related events will be defined as the period of “Date of last visit or contact in the maintenance phase – Date of the first dose of the study drug in the maintenance phase + 1.”

IBDQ score will be handled as follows:

- The questions (Q) on the same day of measurement will be used for calculation of each subscore and total score. After calculating each subscore and total score, the time point will be transferred.
- IBDQ subscore for abdominal symptoms: Mean of Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29 (round off to the first decimal place).
- IBDQ subscore for general condition: Mean of Q2, Q6, Q10, Q14, and Q18 (round off to the first decimal place).
- IBDQ subscore for emotion: Mean of Q3, Q7, Q11, Q15, Q19, Q21, Q23, Q25, Q27, Q30, Q31, and Q32 (round off to the first decimal place).
- IBDQ subscore for social function: Mean of Q4, Q8, Q12, Q16, and Q28 (round off to the first decimal place).
- IBDQ total score: Sum of all questions (round off to the first decimal place).
 - The value of each question after imputing missing data will be used for the calculation of each subscore (abdominal symptoms, general condition, emotion, and social function).
- The handling of missing data in calculation of each subscore (abdominal symptoms, general condition, emotion, and social function) and IBDQ total score will be defined as follows:

Variable	Handling of missing data
IBDQ subscore for abdominal symptoms, IBDQ subscore for general condition, IBDQ subscore for emotion, and IBDQ subscore for social function	<ul style="list-style-type: none"> • If 1 question is missing among those used for calculation of each subscore, the missing data will be imputed using the mean of the non-missing questions used for calculation of that subscore. • If 2 questions are missing among those used for calculation of each subscore, that subscore will be handled as missing.
IBDQ total score	<ul style="list-style-type: none"> • Among the questions used for calculation of IBDQ total score, the missing data will be imputed using the mean of the non-missing questions used for calculation of each subscore. However, if 5 or more questions are missing or 2 or more subscores are missing among the questions used for calculation of IBDQ total score or 3 or more

	questions are missing among those used for calculation of a certain subscore, the total score will be handled as missing.
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- 170 or higher in IBDQ total score: “Yes” if IBDQ total score is ≥ 170 , “No” if it is < 170 , and “Missing” if it is missing.
- -16 or lower in change from Week 10 in IBDQ total score: “Yes” if the change from Week 10 in IBDQ total score is ≤ -16 , “No” if it is > -16 , and “Missing” if it is missing.
- 16 or higher in change from baseline (Week 0) in IBDQ total score: “Yes” if the change from baseline (Week 0) in IBDQ total score is ≥ 16 , “No” if it is < 16 , and “Missing” if it is missing.
- Time to -16 or lower in change from Week 10 in IBDQ total score
 - For subjects who received the study drug in the open-label cohort, IBDQ total scores after Week 10 measured by the day of the first dose of the study drug in the open-label cohort will be used. For subjects who did not receive the study drug in the open-label cohort, all IBDQ total scores after Week 10 will be used.
 - A subject whose IBDQ total score change from Week 10 was ≤ -16 will be treated as an event case, and time to -16 or lower in change from Week 10 in IBDQ total score will be defined as the period of “Earliest date when IBDQ total score change from Week 10 is ≤ -16 – Measuring date of IBDQ total score at Week 10 + 1.”
 - A subject whose IBDQ total score change from Week 10 was never ≤ -16 will be treated as a censored case, and time to -16 or lower in change from Week 10 in IBDQ total score will be defined as the period of “Last measuring date of IBDQ total score – Measuring date of IBDQ total score at Week 10 + 1.”

A prior TNF α antagonist use, concomitant use of immunomodulators at Week 0, and concomitant use of oral corticosteroids at Week 0 will be defined as follows:

- Prior TNF α antagonist use: Subjects coded with at least 1 drug of Preferred Name of Who Drug in the following table for medication history will be classified as “Yes.” All others will be classified as “No.”

Preferred Name
Infliximab
Adalimumab
Golimumab

- Concomitant use of immunomodulators at Week 0: Subjects who received any concomitant medication (for treatment of UC) which is classified as “immunomodulators” in the concomitant medication (for treatment of UC) which was started before the first dose of the

study drug in the induction phase and continued in the induction phase will be classified as “Yes.” All others will be classified as “No.”

- Any concomitant medication (for treatment of UC) which was started after the first dose of the study drug in the induction phase is not subject to this handling.
- Concomitant use of oral corticosteroids at Week 0: Subjects who received any concomitant medication (for treatment of UC) which is classified as “corticosteroids” and whose route of administration is “oral” in the concomitant medication (for treatment of UC) which was started before the first dose of the study drug in the induction phase and continued in the induction phase will be classified as “Yes.” All others will be classified as “No.”
 - Any concomitant medication (for treatment of UC) which was started after the first dose of the study drug in the induction phase is not subject to this handling.
- Concomitant use of oral corticosteroids at Week 10: Regarding the “oral corticosteroid dosage” defined below, subjects whose oral corticosteroid dosage is larger than 0 at Week 10 will be classified as “Yes.” All others will be classified as “No.”

Among concomitant medications (for treatment of UC) in the maintenance phase, the medication which is classified as “corticosteroids” and whose route of administration is “oral” will be classified as “oral corticosteroids” and handled as follows:

- The acceptable window in the table of TIME WINDOW for oral corticosteroid dosage will be handled as follows: For acceptable windows at each visit except for Week 0, the smallest value among the day of the first dose of the study drug in the open-label cohort (defining the day of the first dose of the study drug in the induction phase as Day 1) and upper limit of the acceptable window in the table after excluding missing values will be defined as the upper limit of the acceptable window for subjects who received the study drug in the open-label cohort. If the date of the first dose of the study drug in the open-label cohort is smaller than the lower limit of the acceptable window in the table, the acceptable window at that visit will not be applied.

TIME WINDOW for oral corticosteroid dosage

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	1	=
Week 2	Study Day: 15	2 to 28	=

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 6	Study Day: 43	29 to 56	=
Week 10	Study Day: 71	57 to 84	=
Week 14	Study Day: 99	85 to 112	=
Week 18	Study Day: 127	113 to 140	=
Week 22	Study Day: 155	141 to 168	=
Week 26	Study Day: 183	169 to 196	=
Week 30	Study Day: 211	197 to 224	=
Week 34	Study Day: 239	225 to 252	=
Week 38	Study Day: 267	253 to 280	=
Week 42	Study Day: 295	281 to 308	=
Week 46	Study Day: 323	309 to 336	=
Week 50	Study Day: 351	337 to 364	=
Week 54	Study Day: 379	365 to 392	=
Week 58	Study Day: 407	393 to 413	=
Week 60	Study Day: 421	414 to 448	=
Week 60 (LOCF)		=	=

- Oral corticosteroid dosage at each visit other than Week 60 (LOCF): Oral corticosteroid dosage in each Study Day period will be defined as sum of daily doses of oral corticosteroids (converted dosage of prednisolone) used in each Study Day period. For the Study Day period when oral corticosteroids are not used, daily dose will be “0.” Oral corticosteroid dosage at each visit will be a mean of oral corticosteroid dosage in each Study Day period within the acceptable window of each visit.
- Oral corticosteroid dosage at Week 60 (LOCF): Oral corticosteroid dosage at the last visit during the period from Week 14 to Week 16 will be used, after excluding missing values.
- Corticosteroid-free remission at Week 60: “Corticosteroid-free remission” if concomitant use of corticosteroids at Week 0 is “Yes,” oral corticosteroid dosage at Week 60 is “0 mg/day” and clinical remission at Week 60 is “Clinical remission.” All others will be defined as

“Non-corticosteroid-free remission.”

- For Week 60 of clinical remission at Week 60, the visit after processing “HANDLING OF TIME WINDOW” will be used.

Negative or positive (persistently positive, transiently positive) status of AVA will be determined as follows:

- Persistently positive
 - “Subjects in the induction and maintenance phases who were determined to be AVA-positive in at least 2 consecutive samples sorted by date of blood collection after the day of the first dose of the study drug in the induction phase” or “subjects in the induction and maintenance phases who were determined to be AVA-positive in the latest sample collected after the day of the first dose of the study drug in the induction phase” will be classified as persistently positive.
- Transient positive
 - Subjects in the induction and maintenance phases who do not correspond to “subjects in the induction and maintenance phases who were determined to be AVA-positive in at least 2 consecutive samples sorted by date of blood collection after the day of the first dose of the study drug in the induction phase,” and determined to be AVA-positive in at least one sample collected after the day of the first dose of the study drug in the induction phase will be classified as transiently positive.

Negative or positive status of the neutralizing antibody will be determined as follows:

- “Positive” if the neutralizing antibody is positive for AVA and neutralizing antibody with the same VISIT in each subject. “Negative” if the neutralizing antibody is negative or AVA is negative. Neutralizing antibody will be handled as missing if it does not correspond to any of the above.

AVA in the induction and maintenance phases and neutralizing antibody in the induction and maintenance phases will be defined as follows:

- AVA in the induction and maintenance phases
 - Subjects who were determined to be AVA-positive at any visit after the day of the first dose of the study drug in the induction phase, and in the maintenance phase will be classified as “AVA-positive.” Subjects who were determined to be AVA-negative at all visits (except for those with missing values) after the day of the first dose of the study drug in the induction phase, and in the maintenance phase will be classified as “AVA-negative.” Subjects whose AVA values are missing at all visits in the induction and maintenance phases will be classified as missing.

- Neutralizing antibody in the induction and maintenance phases
 - Subjects who were determined to be positive for neutralizing antibodies at any visit after the day of the first dose of the study drug in the induction phase, and in the maintenance phase will be classified as “Positive for neutralizing antibodies.” Subjects who were determined to be negative for neutralizing antibodies at all visits (except for those with missing values) after the day of the first dose of the study drug in the induction phase, and in the maintenance phase will be classified as “Negative for neutralizing antibodies.” Subjects whose neutralizing antibody values are missing at all visits in the induction and maintenance phases will be classified as missing.

Lymphocytes and neutrophils will be calculated with the following formula:

- $\text{Lymphocytes} = \text{WBC} \times \text{lymphocytes (\%)}$
- $\text{Neutrophils} = \text{WBC} \times \text{neutrophils (\%)}$

1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS

1.1 Disposition of Subjects

1.1.1 Study Information

Analysis set:	All subjects who signed the informed consent form
Analysis	Date first subject signed the informed consent form
variables:	Date of last visit or contact in the maintenance phase, whichever comes later
	MedDRA version
	WHO Drug version
	SAS version used for creating the datasets
Analysis	The following analysis will be performed for the above analysis variables.
methodology:	(1) Display of the analysis variables

1.1.2 Disposition of All Subjects Who Did Not Enter in the Maintenance Phase

Analysis set:	All subjects who achieved clinical response at Week 10 and did not enter in the maintenance phase
Analysis	Categories in parenthesis [] (hereinafter the same)
variables:	
	Age (years) [Min≤ - ≤34, 35≤ - ≤Max]
	[Min≤ - ≤64, 65≤ - ≤Max]
	Gender [Male, Female]
Analysis	The following analysis will be performed for the above analysis variables
methodology:	by each “cohort and treatment group in the induction phase” and in the consolidated “cohorts and treatment groups in the induction phase.”
	(1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.1.3 Subject Eligibility

Analysis set:	Subjects who achieved clinical response at Week 10
Analysis	Eligibility for entering into the [Eligible, Not eligible]
variables:	maintenance phase
Analysis	The following analysis will be performed for the above analysis variables
methodology:	by each cohort and treatment group in the induction phase.
	(1) Frequency distributions

1.1.4 Number of Subjects Who Entered in the Maintenance Phase by Site

Analysis set:	All subjects who entered in the maintenance phase
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Analysis variables:	Eligibility for entering into the maintenance phase	[Eligible]
Stratum:	Study site	[Site numbers will be used as categories]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.”	
	(1) Frequency distributions	

1.1.5 Disposition of Subjects

1.1.5.1 Disposition of Subjects

Analysis set:	All subjects who entered in the maintenance phase	
Analysis variables:	Study drug administration status in the maintenance phase	[Not treated]
	Reason for not being treated	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study drug completion status in the maintenance phase	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study visit completion status in the maintenance phase	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in	

the maintenance phase and subjects in the placebo continuation group.”
 When calculating percentages of the reasons for not being treated, the number of subjects who did not receive the study drug in the maintenance phase will be used as the denominator. When calculating percentages of the reasons for not being completed, the number of subjects who did not completed the study drug/study visit in the maintenance phase will be used as the denominator.

(1) Frequency distributions

1.1.6 Study Drug Completion Status and Study Visit Completion Status

Analysis set:	All subjects who entered in the maintenance phase	
Analysis variables:	Study drug completion status	[Completed, Incompleted]
	in the maintenance phase	
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study visit completion status	[Completed, Incompleted]
	in the maintenance phase	
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Categories:	Duration of study drug exposure in the maintenance phase (days)	[0, 1≤ - ≤56, 57≤ - ≤112, 113≤ - ≤168, 169≤ - ≤224, 225≤ - ≤280, 281≤ - ≤336, 337≤ - ≤392, 393≤ - ≤Max]
	Duration on study after the first dose of the study drug in the maintenance phase (days)	[0, 1≤ - ≤56, 57≤ - ≤112, 113≤ - ≤168, 169≤ - ≤224, 225≤ - ≤280, 281≤ - ≤336, 337≤ - ≤392, 393≤ - ≤Max]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.” Frequency distributions will be provided for study drug completion status in the maintenance phase in the analysis of (1). Frequency distributions will be provided for study visit completion status in the maintenance phase in the analysis of (2).	

- (1) Frequency distribution by duration of study drug exposure in the maintenance phase
- (2) Frequency distribution by duration on study after the first dose of the study drug in the maintenance phase

1.1.7 Protocol Deviations and Analysis Sets

1.1.7.1 Protocol Deviations in the Maintenance Phase

Analysis set:	All subjects who entered in the maintenance phase	
Analysis variables:	Protocol deviations in the maintenance phase	[Major GCP violations, Deviations of protocol entry criteria, Deviations of discontinuation criteria, Deviations related to treatment procedure or dose, Deviations concerning excluded medication or therapy, Deviations to avoid emergency risk, Other]
Analysis methodology:	<p>The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.”</p> <p>Frequency distribution of subjects with protocol deviations in the maintenance phase will be provided for above each deviation category. A subject who has several deviations that can be classified into the same category will be counted once in each appropriate category (overlapped counting).</p>	
	(1) Frequency distributions	

1.1.7.2 Analysis Sets of All Subjects Randomized in the Maintenance Phase

Analysis set:	All subjects randomized in the maintenance phase	
Analysis variables:	Handling of subjects and subject data in the maintenance phase in analysis sets	[Categories are based on the specifications in “Handling Rules for Analysis Data”]
	Inclusion/Exclusion of analysis sets	
	Full analysis set in the maintenance phase	[Included]
	Per protocol set in the maintenance phase	[Included]
Analysis methodology:	The following analyses of (1) and (2) will be performed for the above analysis variables by treatment group in the maintenance phase and the following analysis of (3) will be performed by treatment group in the maintenance phase and in the consolidated treatment groups in the maintenance phase. A subject who corresponds to several categories in (1) and (2) will be counted once in each appropriate category (overlapped counting). (1) Frequency distributions concerning the handling of subjects in the maintenance phase in each analysis set (2) Frequency distributions concerning the handling of subject data in the maintenance phase in each analysis set (3) Frequency distributions concerning the number of subjects included in each analysis set	

1.1.7.3 Analysis Sets of All Subjects Who Entered in the Maintenance Phase

Analysis set:	All subjects who entered in the maintenance phase	
Analysis variables:	Handling of subjects and subject data in the maintenance phase in analysis sets	[Categories are based on the specifications in “Handling Rules for Analysis Data”]
	Inclusion/Exclusion of analysis sets	
	Safety analysis set in the maintenance phase	[Included]

Analysis methodology: The following analyses of (1) and (2) will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and the following analysis of (3) will be performed by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.”

A subject who corresponds to several categories in (1) and (2) will be counted once in each appropriate category (overlapped counting).

- (1) Frequency distributions concerning the handling of subjects in the maintenance phase in each analysis set
- (2) Frequency distributions concerning the handling of subject data in the maintenance phase in each analysis set
- (3) Frequency distributions concerning the number of subjects included in each analysis set

1.2 Demographic and Other Baseline Characteristics

1.2.1 Distribution of Baseline Demographics

Analysis set:	All subjects who entered in the maintenance phase	
Analysis variables:	Age (years)	[Min≤ - ≤34, 35≤ - ≤Max]
		[Min≤ - ≤64, 65≤ - ≤Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg) at Week 0	[Min≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
	BMI (kg/m ²) at Week 0	[Min≤ - ≤18.4, 18.5≤ - ≤24.9, 25.0≤ - ≤Max]
	Smoking classification	[Never smoked, Current smoker, Ex-smoker]
	Duration of UC (years)	[Min≤ - <1, 1≤ - <3, 3≤ - <7, 7≤ - ≤Max, Missing]
	Prior corticosteroid failure	[Yes, No]
	Classification 1 of prior corticosteroid failure	[Resistance, Dependence, Intolerance]
	Classification 2 of prior corticosteroid failure	[Refractory, Intolerance]
	Prior immunomodulator failure	[Yes, No]

Classification of prior immunomodulators failure	[Refractory, Intolerance]
Prior TNF α antagonist failure	[Yes, No]
Number of drugs of TNF α antagonist failure	[1 drug, 2 drugs, 3 drugs, None]
Classification of prior TNF α antagonist failure	[Inadequate response, Loss of response, Intolerance]
Worst prior treatment failures	[Prior TNF α antagonist failure, Prior immunomodulators failure but not TNF α antagonist failure, Prior corticosteroid failure only]
Prior immunomodulators and TNF α antagonist failure	[Yes, No]
Prior TNF α antagonist use	[Yes, No]
Infliximab	[Yes, No]
Adalimumab	[Yes, No]
Golimumab	[Yes, No]
Concomitant use of 5-ASA at Week 0	[Yes, No]
Concomitant use of immunomodulators at Week 0	[Yes, No]
Concomitant use of oral corticosteroids at Week 0	[Yes, No]
No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0	[Yes, No]
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0 (concomitant use of oral corticosteroids only)	[Yes, No]

No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0	[Yes, No]
Complete Mayo score at Week 0	[0≤ - ≤5, 6≤ - ≤8, 9≤ - ≤12]
Disease localization	[Total colitis, Left-sided colitis]
Concurrent extraintestinal manifestations	[Yes, No]
Cohort in the induction phase	[Cohort 1, Cohort 2]
Number of the study drug infusion in the induction phase	[1, 2, 3]
Clinical response at Week 10	[Clinical response, Non-response]
Clinical remission at Week 10	[Clinical remission, Non-remission]
Mucosal healing at Week 10	[Mucosal healing, Non-healing]
Complete Mayo score at Week 10	[0≤ - ≤5, 6≤ - ≤8, 9≤ - ≤12] [0≤ - ≤2, 3≤ - ≤12]
Concomitant use of oral corticosteroids at Week 10	[Yes, No]
Oral corticosteroid dosage (mg/day) at Week 10	[0< - ≤10, 10< - ≤Max]

Analysis methodology: The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.”

(1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.2.2 Medical History, Concurrent Medical Conditions

Analysis set: Safety analysis set in the maintenance phase

Analysis variables: Medical history
Concurrent medical conditions (concurrent extraintestinal manifestations of UC)

Concurrent medical conditions (other than concurrent extraintestinal manifestations of UC)

Analysis methodology: The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.” The analysis variables will be coded by use of MedDRA and will be summarized based on the SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

- (1) Frequency distributions for medical history (by SOC and PT)
- (2) Frequency distributions for concurrent medical conditions (concurrent extraintestinal manifestations of UC) (by SOC and PT)
- (3) Frequency distributions for concurrent medical conditions (other than concurrent extraintestinal manifestations of UC) (by SOC and PT)

The frequency distributions will be provided according to the rules below:
[Number of subjects]

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC.
A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

1.2.3 Medication History, Concomitant Medications in the Maintenance Phase, Concomitant Therapies in the Maintenance Phase

Analysis set:	Safety analysis set in the maintenance phase	
Analysis variables:	Medication history	
	Concomitant medications (for treatment of UC) in the maintenance phase	
	Classification of concomitant medications (for treatment of UC) in the maintenance phase	[5-ASA, Corticosteroids, Immunomodulators, Other]
	Concomitant medications (for treatment of UC) in the maintenance phase that fall under the category of rescue treatments	
	Classification of concomitant medications (for treatment of UC) in the maintenance phase that fall under the category of rescue treatments	[5-ASA, Corticosteroids, Immunomodulators,

Other]

Concomitant medications (for other than treatment of UC) in the maintenance phase

Concomitant therapies in the maintenance phase [Yes, No]

Concomitant therapies in the maintenance phase [Yes, No] that fall under the category of rescue treatments

Analysis methodology: The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated “treatment groups in the maintenance phase and subjects in the placebo continuation group.” Medication history, concomitant medications (for treatment of UC) in the maintenance phase, concomitant medications (for treatment of UC) in the maintenance phase that fall under the category of rescue treatments, and concomitant medications (for other than treatment of UC) in the maintenance phase will be coded by use of WHO Drug and summarized based on Preferred Name, which will be sorted in decreasing frequency. A subject who has been administered several medications with the same Preferred Name will be counted only once for that Preferred Name.

- (1) Frequency distributions for medication history
- (2) Frequency distributions for concomitant medications (for treatment of UC) in the maintenance phase that were ongoing at the first dose of the study drug in the maintenance phase and continued in the maintenance phase, and concomitant medications (for treatment of UC) in the maintenance phase that started after the first dose of the study drug in the maintenance phase by category
- (3) Frequency distributions for concomitant medications (for treatment of UC) in the maintenance phase that fall under the category of rescue treatments, were ongoing at the first dose of the study drug in the maintenance phase and continued in the maintenance phase, and concomitant medications (for treatment of UC) in the maintenance phase that fall under the category of rescue treatments and started after the first dose of the study drug in the maintenance phase by category
- (4) Frequency distributions for concomitant medications (for other than treatment of UC) in the maintenance phase that were ongoing at the first dose of the study drug in the maintenance phase and continued in the maintenance phase, and concomitant medications (for other than treatment of UC) in the maintenance phase that started after the first

dose of the study drug in the maintenance phase

- (5) Frequency distributions for presence or absence of concomitant therapies in the maintenance phase that were ongoing at the first dose of the study drug in the maintenance phase and continued in the maintenance phase, and concomitant therapies in the maintenance phase that started after the first dose of the study drug in the maintenance phase
- (6) Frequency distributions for presence or absence of concomitant therapies in the maintenance phase that fall under the category of rescue treatments, were ongoing at the first dose of the study drug in the maintenance phase and continued in the maintenance phase, and concomitant therapies in the maintenance phase that fall under the category of rescue treatments and started after the first dose of the study drug in the maintenance phase

1.3 Measurement of Compliance Status for Treatment

1.3.1 Study Drug Exposure and Compliance in the Maintenance Phase

Analysis set:	Safety analysis set in the maintenance phase	
Analysis variables:	Duration of study drug exposure in the maintenance phase (days)	[1≤ - ≤56, 57≤ - ≤112, 113≤ - ≤168, 169≤ - ≤224, 225≤ - ≤280, 281≤ - ≤336, 337≤ - ≤392, 393≤ - ≤Max]
	Duration on study after the first dose of the study drug in the maintenance phase (days)	[1≤ - ≤56, 57≤ - ≤112, 113≤ - ≤168, 169≤ - ≤224, 225≤ - ≤280, 281≤ - ≤336, 337≤ - ≤392, 393≤ - ≤Max]
	Number of the study drug infusion in the maintenance phase (times)	[1, 2, 3, 4, 5, 6]
	Number of completed infusions of the study drug in the maintenance phase (times)	[0, 1, 2, 3, 4, 5, 6]
	Number of completed or incompleted infusions in total infusions in the maintenance phase	[Completed, Incompleted]
Analysis methodology:	The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group” and in the consolidated	

“treatment groups in the maintenance phase and subjects in the placebo continuation group.”

(1) Frequency distributions for categorical variables and summary statistics for continuous variables

In the frequency distributions for number of completed or incompleting infusions in total infusions in the maintenance phase, the sum of the number of completed infusions in the maintenance phase in the applicable treatment group will be counted as frequency for “Completed” and the sum of the number of incompleting infusions will be counted as frequency for “Incompleting.” When calculating percentage, the sum of the number of completed infusions and the number of incompleting infusions (i.e., number of total infusions in the maintenance phase) will be used as the denominator.

2 EFFICACY ANALYSIS

The “full analysis set in the maintenance phase” based on the specifications in the protocol and the “Handling Rules for Analysis Data” will be the main analysis set. For the sensitivity point of view, the “per protocol set in the maintenance phase” will be used for an analysis performed secondarily on the primary endpoint in order to examine the robustness of the results.

2.1 Primary Endpoints and Analysis Methodology

2.1.1 Primary Analysis

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
Stratum:	Prior TNF α antagonist use	[Yes, No]

Analysis methodology: The following analysis will be performed in the “full analysis set in the maintenance phase.”

Frequency distributions will be provided for “clinical remission at Week 60” (the primary endpoint of the maintenance phase) by treatment group in the maintenance phase along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated. The similar calculation will be performed with stratification according to the “prior TNF α antagonist use.” The Cochran-Mantel-Haenszel (CMH) test will be performed using the “prior TNF α antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy.

The results of the primary analysis of the maintenance phase will be interpreted as below to determine the efficacy of MLN0002 maintenance therapy.

- The superiority of MLN0002 over the placebo on clinical remission at Week 60 in the primary analysis of the maintenance phase will be demonstrated when a statistically significant difference is observed in the clinical remission at Week 60.

2.1.2 Secondary Analysis

Analysis set: Full analysis set in the maintenance phase

Per protocol set in the maintenance phase

Analysis variables: Clinical remission at Week 60 [Clinical remission, Non-remission]

Stratum: Prior TNF α antagonist use [Yes, No]

Analysis methodology: For the sensitivity point of view, the following analysis will be performed to examine the robustness of the results.

(1) The clinical remission at Week 60 using the scores of findings on endoscopy based on the adjudication results in the study site will be analyzed in the same manner as those in the primary analysis in 2.1.1 in the “per protocol set in the maintenance phase.”

(2) The clinical remission at Week 60 using the scores of findings on endoscopy based on adjudication of the Clinical Endpoint Committee (CEC) will be analyzed in the same manner as those in the primary analysis in 2.1.1 in the “full analysis set in the maintenance phase.”

The following analysis will be performed for reference.

(3) For the clinical remission at Week 60 using the scores of findings on endoscopy based on the adjudication results in the study site, the CMH adjusted risk difference (MLN0002 group – placebo group) with the “prior TNF α antagonist use” as a stratification factor and the 95% two-sided CI will be calculated in the “full analysis set in the maintenance phase.”

(4) The clinical remission at Week 60 using the scores of findings on endoscopy based on the adjudication results in the study site will be analyzed in the same manner as those in the primary analysis in 2.1.1 in the “full analysis set in the maintenance phase” after excluding the subjects whose complete Mayo scores at Week 60 are missing.

2.2 Secondary Endpoints and Analysis Methodology

Analysis set: Full analysis set in the maintenance phase
Subjects who were receiving oral corticosteroids concomitantly at Week 0 in the full analysis set in the maintenance phase

Analysis variables: Durable response [Durable response, Non-durable response]

Mucosal healing at Week 60 [Mucosal healing, Non-healing]

Durable remission [Durable remission, Non-durable]

		remission]
	Corticosteroid-free remission at Week 60	[Corticosteroid-free remission, Non-corticosteroid-free remission]
Stratum:	Prior TNF α antagonist use	[Yes, No]
Analysis methodology:	<p>The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase.</p> <p>Corticosteroid-free remission at Week 60 will be analyzed in “subjects who were receiving corticosteroids concomitantly at Week 0 in the full analysis set in the maintenance phase.” All other variables will be analyzed in the “full analysis set in the maintenance phase.”</p> <p>(1) Frequency distributions will be provided for each analysis variable using the scores of findings on endoscopy based on the adjudication results in the study site along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.</p> <p>(2) Frequency distributions will be provided for each analysis variable using the scores of findings on endoscopy based on the adjudication results in the study site with the “prior TNFα antagonist use” as a stratification factor along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.</p> <p>(3) The CMH test will be performed for each analysis variable using the scores of findings on endoscopy based on the adjudication results in the study site with the “prior TNFα antagonist use” as a stratification factor to calculate the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. Also, the CMH adjusted risk difference (MLN0002 group – placebo group) with the “prior TNFα antagonist use” as a stratification factor and the 95% two-sided CI will be calculated.</p> <p>(4) Each analysis variable using the scores of findings on endoscopy based on adjudication of the CEC will be analyzed in the same manner as those in 2.2 (1) to (3).</p>	

2.3 Other Endpoints and Analysis Methodology

2.3.1 Endpoints Related to Mayo Scores

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	Clinical remission at Week 60 and mucosal healing at Week 60 in the sub-population of subjects without prior TNF α antagonist use and in the sub-population of subjects who had failed with a TNF α antagonist	[Clinical remission, Non-remission] [Mucosal healing, Non-healing]
	Clinical remission at Week 60 and mucosal healing at Week 60 in the sub-population of subjects who had failed with a corticosteroid monotherapy and an immunomodulator (except those had failed with a TNF α antagonist)	[Clinical remission, Non-remission] [Mucosal healing, Non-healing]
	Partial Mayo scores	
	Partial Mayo score change from baseline (Week 0)	
	Partial Mayo score change from Week 10	
	Clinical response based on partial Mayo score	[Clinical response, Non-response]
	Complete Mayo score	
	Complete Mayo score change from baseline (Week 0)	
	Complete Mayo score change from Week 10	
	Each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy, and physician's global assessment)	[0, 1, 2, 3]
	Change in each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy, and physician's global assessment) from baseline (Week 0)	
	0 in the subscore for the findings on endoscopy	[Yes, No]
Visit:	Weeks 0, 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60 (LOCF) (partial Mayo score, each Mayo subscore [stool frequency, rectal bleeding, and physician's global assessment])	
	Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60 (LOCF) (partial Mayo score change from baseline [Week 0], change in each Mayo subscore [stool frequency, rectal bleeding, and physician's global assessment] from baseline [Week 0])	
	Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, and 60 (clinical response based on partial Mayo score)	

Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60

(LOCF) (partial Mayo score change from Week 10)

Weeks 0, 10, and 60 (complete Mayo score, Mayo subscore [findings on endoscopy])

Weeks 10 and 60 (complete Mayo score change from baseline [Week 0], change in Mayo subscore (findings on endoscopy) from baseline [Week 0], 0 in the subscore for the findings on endoscopy)

Analysis methodology: The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy for analyses (1) to (12).

- (1) Frequency distributions will be provided for the clinical remission at Week 60 and mucosal healing at Week 60 in the sub-population of subjects without prior TNF α antagonist use along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (2) Frequency distributions will be provided for the clinical remission at Week 60 and mucosal healing at Week 60 in the sub-population of subjects who had failed with a TNF α antagonist along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (3) Frequency distributions will be provided for the clinical remission at Week 60 and mucosal healing at Week 60 in the sub-population of subjects who had failed with a corticosteroid monotherapy along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (4) Frequency distributions will be provided for the clinical remission at Week 60 and mucosal healing at Week 60 in the sub-population of subjects who had failed with an immunomodulator (except those had failed with a TNF α antagonist) along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided

CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.

- (5) Summary statistics and 95% two-sided CI of the mean will be calculated for partial Mayo scores at each visit.
- (6) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in partial Mayo score from baseline (Week 0) at each visit, and also, the point estimate and 95% two-sided CI for the difference in the mean between treatment groups (MLN0002 group – placebo group) will be calculated.
- (7) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in partial Mayo score from Week 10 at each visit, and also, the point estimate and 95% two-sided CI for the difference in the mean between treatment groups (MLN0002 group – placebo group) will be calculated.
- (8) Frequency distributions will be provided for clinical response based on partial Mayo score at each visit along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated.
- (9) Summary statistics and 95% two-sided CI of the mean will be calculated for complete Mayo scores at each visit.
- (10) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in complete Mayo score from baseline (Week 0) at each visit.
- (11) The point estimate and 95% two-sided CI for the difference in the least square (LS) mean between treatment groups (MLN0002 group – placebo group) will be calculated using the analysis of covariance (ANCOVA) model with changes in complete Mayo score from baseline (Week 0) at Week 60 as a response, the treatment groups in the maintenance phase and “prior TNF α antagonist use” as factors, and complete Mayo score at Week 0 as a covariate.
- (12) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in complete Mayo score from Week 10 at Week 60, and also, the point estimate and 95% two-sided CI for the difference in the mean between treatment groups (MLN0002 group – placebo group) will be calculated.
- (13) Summary statistics and 95% two-sided CI of the mean will be calculated

for each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy [adjudication results in the study site], findings on endoscopy [adjudication of the CEC], and physician’s global assessment) at each visit.

- (14) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy [adjudication results in the study site], findings on endoscopy [adjudication of the CEC], and physician’s global assessment) from baseline (Week 0) at each visit.
- (15) Frequency distributions will be provided for each Mayo subscore (stool frequency, rectal bleeding, findings on endoscopy [adjudication results in the study site], findings on endoscopy [adjudication of the CEC], and physician’s global assessment) at each visit.
- (16) Frequency distributions will be provided for the proportion of 0 in the subscore for the findings on endoscopy using the scores based on the adjudication results in the study site at each visit along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be also calculated. A similar analysis will be performed using the scores for the findings on endoscopy based on adjudication of the CEC.

2.3.2 Endpoints Related to IBDQ

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	IBDQ scores (total score and each subscore [abdominal symptoms, general condition, emotion, and social function])	
	Change in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function]) from Week 14	
	Change in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function]) from Week 10	
	Change in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function]) from baseline (Week 0)	
	IBDQ total score ≥ 170	[Yes, No]

	Change in IBDQ total score from baseline (Week 0) ≥ 16 [Yes, No]
	Change in IBDQ total score from Week 10 ≤ -16 [Yes, No]
	Time to -16 or lower in change from Week 10 in IBDQ total score
Visit:	Weeks 0, 10, 14, 38, 60, and Week 60 (LOCF) (IBDQ score)
	Weeks 38, 60, and Week 60 (LOCF) (change in IBDQ score from Week 14)
	Weeks 14, 38, 60, and Week 60 (LOCF) (change in IBDQ score from Week 10, and change in IBDQ total score from Week 10 ≤ -16)
	Weeks 10, 14, 38, 60, and Week 60 (LOCF) (IBDQ total score ≥ 170 , change in IBDQ score from baseline [Week 0], change in IBDQ total score from baseline [Week 0] ≥ 16 , change in IBDQ total score from baseline [Week 0] ≤ 16)
Analysis methodology:	The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase.
	(1) Summary statistics and 95% two-sided CI of the mean will be calculated for IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at each visit.
	(2) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) from Week 14 at each visit.
	(3) The point estimate and 95% two-sided CI for the difference in the least square (LS) mean between treatment groups (MLN0002 group – placebo group) will be calculated using the analysis of covariance (ANCOVA) model with changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) from Week 14 at Week 60 (LOCF) as a response, the treatment groups in the maintenance phase as a factor, and Week 14 values that correspond to the scores used as response as a covariate.
	(4) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) from Week 10 at each visit.
	(5) The point estimate and 95% two-sided CI for the difference in the least square (LS) mean between treatment groups (MLN0002 group – placebo group) will be calculated using the analysis of covariance (ANCOVA) model with changes in IBDQ total scores and each

subscore (abdominal symptoms, general condition, emotion, and social function) from Week 10 at Week 60 (LOCF) as a response, treatment groups in the maintenance phase as a factor, and Week 10 values that correspond to scores used as response as a covariate.

- (6) Summary statistics and 95% two-sided CI of the mean will be calculated for changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) from baseline (Week 0) at each visit.
- (7) The point estimate and 95% two-sided CI for the difference in the least square (LS) mean between treatment groups (MLN0002 group – placebo group) will be calculated using the analysis of covariance (ANCOVA) model with changes in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) from baseline (Week 0) at Week 60 (LOCF) as a response, treatment groups in the maintenance phase as a factor, and Week 0 values that correspond to scores used as response as a covariate.
- (8) Frequency distributions will be provided for the proportion of subjects whose IBDQ total score at each visit is ≥ 170 in subjects whose IBDQ total score at baseline (Week 0) is < 170 among the full analysis set in the maintenance phase along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group – placebo group) will be calculated. The Pearson's chi-square test will be also performed at Week 60 (LOCF).
- (9) Frequency distributions will be provided for subjects whose IBDQ total score change from baseline (Week 0) is ≥ 16 and subjects whose IBDQ total score change from Week 10 is ≤ -16 at each visit along with the point estimate and 95% two-sided CI for the proportions of subjects whose IBDQ total score change from baseline (Week 0) is ≥ 16 and subjects whose IBDQ total score change from Week 10 is ≤ -16 at each visit. The point estimate and 95% two-sided CI for the difference in each proportion between treatment groups (MLN0002 group – placebo group) at each visit will be calculated. The Pearson's chi-square test will be also performed at Week 60 (LOCF).
- (10) The cumulative survival rate on the onset date of "change in IBDQ total score from Week 10 ≤ -16 " will be calculated and plotted by treatment group using the Kaplan-Meier method, and a log-rank test will be

performed. The time to events (unit=day) will be summarized (25, 50, and 75 percentiles) and CIs for 25, 50, and 75 percentiles will be provided, respectively. Also, the cumulative survival rate of each event will be calculated at 6 months (183 days) and 12 months (365 days).

(11) For the time to -16 or lower in change from Week 10 in IBDQ total score, the hazard ratio of the MLN0002 group against the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI will be calculated using the Cox regression model with treatment group as explanatory variable.

2.3.3 Endpoints Related to Oral Corticosteroid Dosage

Analysis set: Subjects who were receiving corticosteroids concomitantly at Week 0 in the full analysis set in the maintenance phase

Analysis variables: Oral corticosteroid dosage change from Week 10

Visit: Weeks 0, 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60 (LOCF) (oral corticosteroid dosage)

Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60 (LOCF) (oral corticosteroid dosage change from Week 10)

Analysis methodology: The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase.

- (1) Summary statistics and 95% two-sided CI of the mean will be calculated for oral corticosteroid dosage at each visit.
- (2) Summary statistics and 95% two-sided CI of the mean will be calculated for oral corticosteroid dosage change from Week 10 at each visit, and also, the point estimate and 95% two-sided CI for the difference in the mean between treatment groups (MLN0002 group – placebo group) will be calculated.

2.3.4 Endpoints Related to Time to Event

Analysis set: Full analysis set in the maintenance phase

Analysis variables: Time to disease worsening

Time to treatment failure

Time to major UC-related events (UC-related hospitalization, enterectomy)

Stratum: Prior TNF α antagonist use [Yes, No]

Analysis methodology: The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase.

- (1) The cumulative survival rate on the onset date of each event will be calculated and plotted by treatment group using the Kaplan-Meier method. The time to events (unit=day) will be summarized (25, 50, and 75 percentiles) and CIs for 25, 50, and 75 percentiles will be provided, respectively. Also, the cumulative survival rate of each event will be calculated at 6 months (183 days) and 12 months (365 days).
- (2) A stratified log-rank test with “prior TNF α antagonist use” as stratification factor will be performed.
- (3) The hazard ratio of the MLN0002 group against the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI will be calculated using the stratified Cox regression model with treatment group as independent variable and “prior TNF α antagonist use” as stratification factor.

2.4 Analysis of Subjects in the Placebo Continuation Group

Analysis set:	Subjects in the placebo continuation group	
	Subjects who were receiving corticosteroids concomitantly at Week 0 in the placebo continuation group	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
	Durable response	[Durable response, Non-durable response]
	Mucosal Healing at Week 60	[Mucosal healing, Non-healing]
	Durable remission	[Durable remission, Non-durable remission]
	Corticosteroid-free remission at Week 60	[Corticosteroid-free remission, Non-corticosteroid-free remission]
	Complete Mayo score	
	Complete Mayo score change from Week 10	
	IBDQ score (total score)	
	Change in IBDQ score (total score) from Week 14	
Visit:	Weeks 0, 10, 14, 38, 60, and Week 60 (LOCF) (IBDQ score)	
	Weeks 38, 60, and Week 60 (LOCF) (change in IBDQ score from Week 14)	

Weeks 0, 10, and 60 (complete Mayo score)

Weeks 10 and 60 (complete Mayo score change from baseline [Week 0])

Analysis methodology: The following analysis will be performed for the above analysis variables. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy. Corticosteroid-free remission at Week 60 will be analyzed in “subjects who were receiving corticosteroids concomitantly at Week 0 in the placebo continuation group.” All other variables will be analyzed in “subjects in the placebo continuation group.”

- (1) Frequency distributions will be provided for the clinical remission at Week 60 along with the point estimate and 95% two-sided CI for the proportion.
- (2) Frequency distributions will be provided for the durable response along with the point estimate and 95% two-sided CI for the proportion.
- (3) Frequency distributions will be provided for the mucosal healing at Week 60 along with the point estimate and 95% two-sided CI for the proportion.
- (4) Frequency distributions will be provided for corticosteroid-free remission at Week 60 along with the point estimate and 95% two-sided CI for the proportion.
- (5) Summary statistics and 95% two-sided CI of the mean will be calculated for complete Mayo scores at each visit.
- (6) Summary statistics and 95% two-sided CI of the mean will be calculated for complete Mayo score change from baseline (Week 0) at each visit.
- (7) Summary statistics and 95% two-sided CI of the mean will be calculated for IBDQ total score at each visit.
- (8) Summary statistics and 95% two-sided CI of the mean will be calculated for change in IBDQ total score from Week 14 at each visit.

2.5 Statistical and Analytical Issues

2.5.1 Adjustments for Covariates

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
Adjustment factors:	Prior TNF α antagonist use	[Yes, No]
	Concomitant use of immunomodulators at Week 0	[Yes, No]
	Concomitant use of oral corticosteroids at	[Yes, No]

	Week 0	
	Cohort in the induction phase	[Cohort 1, Cohort 2]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
	Complete Mayo score at Week 0	[0 ≤ - ≤ 8, 9 ≤ - ≤ 12]
	Complete Mayo score at Week 10	[0 ≤ - ≤ 2, 3 ≤ - ≤ 12]
	Prior corticosteroid failure	[Yes, No]
Analysis methodology:	Influences of above adjustment factors on odds ratios for the clinical remission at Week 60 will be investigated with following analyses.	

By performing the CMH test using the above adjustment factors as stratification factors and providing adjusted odds ratios of the MLN0002 group compared to the placebo group (MLN0002 group/placebo group) along with the 95% two-sided CI estimates, adjusted odds ratios for clinical remission at Week 60 after adjusting influence of stratification factors will be investigated. In addition, interactions between treatment and adjustment factors will be investigated using the Breslow-Day test.

2.5.2 Handling of Dropouts or Missing Data

The efficacy endpoints of clinical response, clinical remission, or mucosal healing will be considered as non-response, non-remission, or non-healing, when adjudication for these endpoints is missing at that visit.

For other endpoints, missing test results and ineligible data according to the “Handling Rules for Analysis Data” or the SAP will be excluded from statistical analyses and estimations.

Values below the limit of quantification will be handled as 0.

2.5.3 Interim Analyses and Data Monitoring

No interim analyses will be performed for the induction and maintenance phases.

In the open-label cohort, the data for the marketing application as fixed on the cut-off date will be analyzed after fixing the data of all subjects fixed on the cut-off date for the marketing application. Continuation/termination of the study, and change in clinical trial plan, and so on will not be judged based on the analysis.

2.5.4 Multicenter Studies

Although this is a multicenter study, interactions between treatment and study site will not be investigated since the target number of subjects per study site is not sufficiently large for meaningful analyses of the interactions.

2.5.5 Multiple Comparisons/Multiplicity

Since the study has different objectives in the induction and maintenance phases, no adjustments for multiplicity will be performed between the analyses of the two phases setting the significance level at 5% each.

In the maintenance phase, the main focuses will be placed on the results of the CMH test performed for the primary endpoint in the maintenance phase defined as clinical remission at Week 60 in the “full analysis set in the maintenance phase.” Other analytical results will be interpreted to support the results of the primary endpoint or to explore the characteristics of efficacy of MLN0002. These results will be considered one measure suggesting the trends or characteristics of efficacy. Thus, no adjustment for multiplicity will be performed.

2.5.6 Use of an “Efficacy Subset of Subjects”

To confirm the robustness of the primary analysis results for the primary endpoint for the sensitivity point of view, the same analysis as for the “full analysis set in the maintenance phase” will be performed secondarily in the “per protocol set in the maintenance phase.”

2.5.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority

Not applicable.

2.5.8 Examination of Subgroups

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
Stratum:	Age (years)	[Min \leq - \leq 34, 35 \leq - \leq Max] [Min \leq - \leq 64, 65 \leq - \leq Max]
	Gender	[Male, Female]
	Duration of UC (years)	[Min \leq - $<$ 7, 7 \leq - \leq Max]
	Prior corticosteroid failure	[Yes, No]
	Prior immunomodulator failure	[Yes, No]
	Prior TNF α antagonist failure	[Yes, No]
	Number of drugs of TNF α antagonist failure	[1 drug, 2 drugs, 3 drugs, None]
	Classification of prior TNF α antagonist failure	[Inadequate response, Loss of response, Intolerance]
	Worst prior treatment failures	[Prior TNF α antagonist failure, Prior immunomodulators failure but not

	TNF α antagonist failure, Prior corticosteroid failure only]
Prior immunomodulators and TNF α antagonist failure	[Yes, No]
Concomitant use of immunomodulators at Week 0	[Yes, No]
Concomitant use of oral corticosteroids at Week 0	[Yes, No]
No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0	[Yes, No]
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0 (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0	[Yes, No]
Complete Mayo score at Week 0	[0 \leq - \leq 8, 9 \leq - \leq 12]
Cohort in the induction phase	[Cohort 1, Cohort 2]
Complete Mayo score at Week 10	[0 \leq - \leq 2, 3 \leq - \leq 12]
Clinical remission at Week 10	[Clinical remission, Non-remission]
Disease localization	[Total colitis, Left-sided colitis]
Weight (kg) at Week 0	[Min \leq - \leq 59.9, 60.0 \leq - \leq Max]

Analysis methodology: The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy.

- (1) Frequency distributions will be provided along with the point estimate and 95% two-sided CI for the proportion. The point estimate and 95% two-sided CI for the difference in the proportion between treatment

groups (MLN002 group – placebo group) will be also calculated.

3 SAFETY ANALYSIS

3.1 Treatment-Emergent Adverse Event

3.1.1 Overview of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set in the maintenance phase	
Analysis variables:	TEAEs in the maintenance phase	
Categories:	Causality	[Related, Not related]
	Intensity	[Mild, Moderate, Severe]
Analysis methodology:	The following summaries will be provided for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group.”	

- (1) Overview of TEAEs in the maintenance phase
 - 1) All TEAEs in the maintenance phase (number of events, number and percentage of subjects)
 - 2) Causal relationship between all TEAEs in the maintenance phase and study drug (number of events, number and percentage of subjects)
 - 3) Intensity of all TEAEs in the maintenance phase (number of events, number and percentage of subjects)
 - 4) TEAEs in the maintenance phase leading to study drug discontinuation (number of events, number and percentage of subjects)
 - 5) Serious TEAEs in the maintenance phase (number of events, number and percentage of subjects)
 - 6) Causal relationship between serious TEAEs in the maintenance phase and study drug (number of events, number and percentage of subjects)
 - 7) Serious TEAEs in the maintenance phase leading to study drug discontinuation (number of events, number and percentage of subjects)
 - 8) TEAEs in the maintenance phase leading to death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below:

[Number of subjects]

- In the case of “summaries by causality”
A subject with occurrences of TEAE in both categories (i.e., “Related” and “Not related”) will be counted once in the “Related” category.

- In the case of “summaries by intensity”

A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- In the case of summaries other than the above

A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

3.1.2 Displays of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set in the maintenance phase	
Analysis variables:	TEAEs in the maintenance phase	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of onset (day)	[1≤ - ≤56, 57≤ - ≤112, 113≤ - ≤168, 169≤ - ≤224, 225≤ - ≤280, 281≤ - ≤336, 337≤ - ≤392, 393≤ - ≤Max]
	Study drug administration in the maintenance phase (times)	[1, 2, 3, 4, 5, 6]
Analysis methodology:	<p>The following summaries will be provided for the above analysis variables using frequency distributions by each “treatment group in the maintenance phase and subjects in the placebo continuation group.”</p> <p>TEAEs will be coded by use of MedDRA and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.</p> <p>Categories for time of onset (day) will be determined based on the number of days by defining the day of the first dose of the study drug in the maintenance phase as day 1.</p> <ol style="list-style-type: none"> (1) All TEAEs in the maintenance phase by SOC and PT (2) All TEAEs in the maintenance phase by SOC (3) All TEAEs in the maintenance phase by PT (4) Drug-related TEAEs in the maintenance phase by SOC and PT (5) Intensity of all TEAEs in the maintenance phase by SOC and PT (6) Intensity of drug-related TEAEs in the maintenance phase by SOC 	

and PT

- (7) TEAEs in the maintenance phase leading to study drug discontinuation by SOC and PT
- (8) Serious TEAEs in the maintenance phase by SOC and PT
- (9) Serious drug-related TEAEs in the maintenance phase by SOC and PT
- (10) All TEAEs in the maintenance phase by SOC and PT over time
- (11) Infusion reaction in the maintenance phase by SOC and PT
- (12) Infusion reaction in the maintenance phase by study drug administration in the maintenance phase (times) by SOC and PT
- (13) TEAEs in the maintenance phase whose onset date is the day of the study drug administration or the following day by SOC and PT
- (14) TEAEs in the maintenance phase whose onset date is the day of the study drug administration or the following day by study drug administration in the maintenance phase (times) by SOC and PT
- (15) TEAEs in the maintenance phase whose incidence summarized by PT is 3% or higher in either treatment group or subjects in the placebo continuation group by SOC and PT

The frequency distribution and incidence will be provided according to the rules below:

[Number of subjects]

- In the case of “summaries by SOC and PT, by SOC, and by PT”
A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.
Percentages of TEAE in the maintenance phase will be based on the number of subjects in the safety analysis set in the maintenance phase.
- In the case of “summaries of intensity by SOC and PT”
A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.
Percentages of TEAE in the maintenance phase will be based on the number of subjects in the safety analysis set in the maintenance phase.
- In the case of “summaries by SOC and PT over time”
A subject with a TEAE that occurs in more than one interval is

counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE in the maintenance phase for each time interval, the number of subjects at risk (i.e., “subjects who either have an exposure in the study or have an occurrence of TEAE in the maintenance phase, during or after the corresponding time interval”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAEs in the maintenance phase is within the time interval” will be used as the numerator.

- In the case of “summaries of the study drug administration in the maintenance phase (times) by SOC and PT”

A subject with a TEAE that occurs in more than one time of study drug administration is counted for all the administrations (times) that the TEAE occurs. For each administration, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE in the maintenance phase for each administration (time) in the maintenance phase, the number of subjects at risk (i.e., “subjects who received the first, etc., study drug administration in the maintenance phase”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAEs in the maintenance phase is at the time of first, etc., administration in the maintenance phase” will be used as the numerator.

3.2 Pretreatment Event

3.2.1 Displays of Pretreatment Events

Not applicable.

3.3 Clinical Laboratory Evaluations and Other Safety Endpoints

3.3.1 Clinical Laboratory Evaluations

3.3.1.1 Hematology and Blood Biochemistry

Analysis set:	Safety analysis set in the maintenance phase		
Analysis	Hematology		
variables:	Red blood cells (RBC)	White blood cells (WBC)	Hemoglobin
	Hematocrit	Platelets	

WBC differentials (neutrophils/leukocytes, eosinophils/leukocytes, basophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes)

Blood biochemistry

Albumin	AST(GOT)	ALT(GPT)
ALP	Amylase	Glucose
Total bilirubin	Total protein	γ -GTP
Total cholesterol	Triglyceride	Creatinine
BUN	Uric acid	Potassium
Sodium	Calcium	Phosphorus
Magnesium	Chloride	

Inflammatory markers

C-reactive protein (CRP)

Categories: Adjudication results based on normal reference range [Below lower limit of normal range, Within normal range, Over upper limit of normal range]

Categories in SAP Appendix 2 (1)

Visit: Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 60, and 16 weeks after the last dose of the study drug (hematology, blood biochemistry)

Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, and 60 (inflammatory markers)

Analysis methodology: The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group.”

The subjects who received the study drug in the open-label cohort will be excluded from the analysis at 16 weeks after the last dose.

Refer to Appendix 2 of this SAP for laboratory test items subject to this analysis, categories in the shift table, MAV criteria, and definition of elevated liver enzyme.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration for each visit
- (2) Case plots
- (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each post-baseline visit
- (4) Shift tables showing categories of SAP Appendix 2 (1) at Week 0 and each post-baseline visit
- (5) Overall frequency distributions of MAV in the maintenance phase
- (6) Overall frequency distributions of elevated liver enzymes in the

maintenance phase

3.3.1.2 Urinalysis

Analysis set: Safety analysis set in the maintenance phase

Analysis variables: pH
Urine specific gravity
Glucose
Protein
Occult blood
Bilirubin
Ketone body

Categories: Adjudication results [Below lower limit of normal range, Within normal range, Over upper limit of normal range]
based on normal reference range

Visit: Weeks 0, 10, 14, 60, and 16 weeks after the last dose of the study drug

Analysis methodology: The following analyses of (1), (2), and (3) will be performed for pH and specific gravity by each “treatment group in the maintenance phase and subjects in the placebo continuation group.” The following analysis of (3) will be performed for the above analysis variables other than pH and specific gravity by each “treatment group in the maintenance phase and subjects in the placebo continuation group.”
The subjects who received the study drug in the open-label cohort will be excluded from the analysis at 16 weeks after the last dose.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration
- (2) Case plots
- (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each post-baseline visit

3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety

3.3.2.1 Vital Signs, Body Weight

Analysis set: Safety analysis set in the maintenance phase

Analysis variables: Systolic blood pressure
Diastolic blood pressure
Pulse
Body temperature
Weight

Visit: Weeks 0, 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and 16 weeks after the last dose of the study drug

Analysis methodology: The following analysis will be performed for the above analysis variables by each “treatment group in the maintenance phase and subjects in the placebo continuation group.”

The subjects who received the study drug in the open-label cohort will be excluded from the analysis at 16 weeks after the last dose.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration for each visit
- (2) Case plots

3.3.2.2 12-Lead ECG

Analysis set: Safety analysis set in the maintenance phase

Analysis variables: Findings of 12-lead ECG [Within normal limits, Abnormal but not clinically significant, Abnormal and clinically significant]

Visit: Weeks 0, 10, 60, and 16 weeks after the last dose of the study drug

Analysis methodology: The following analysis will be performed for the findings of 12-lead ECG by each “treatment group in the maintenance phase and subjects in the placebo continuation group.”

The subjects who received the study drug in the open-label cohort will be excluded from the analysis at 16 weeks after the last dose.

- (1) Shift tables at Week 0 and each post-baseline visit

3.4 Display of Treatment-Emergent Adverse Event (in Japanese)

Analysis set: Safety analysis set in the maintenance phase

Analysis variables: TEAE in the maintenance phase by SOC and PT

Analysis methodology: Infusion reaction in the maintenance phase by SOC and PT

The similar summaries as 3.1.2 section will be provided for the above analysis variables. SOC and PT will be displayed in Japanese.

4 PHARMACOKINETIC ANALYSIS

4.1 Analysis of Serum Concentrations of MLN0002

- Analysis set: Subjects who underwent proper determination of serum concentrations of MLN0002 in the “full analysis set in the maintenance phase”
- Analysis variables: Serum concentrations of MLN0002
- Visit: Weeks 2, 6, 10, 14, 22, 30, and 60
- Analysis methodology: The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase. When calculating geometric mean and geometric CV%, the analysis will be performed by excluding the data for which serum concentration of MLN0002 is 0.
- (1) Summary statistics, geometric mean, and geometric CV%
 - (2) Mean/standard deviation plot

4.2 Serum Concentrations of MLN0002 by Efficacy Endpoints

- Analysis set: Subjects who underwent proper determination of serum concentrations of MLN0002 in the “full analysis set in the maintenance phase”
- Analysis variables: Serum concentrations of MLN0002
- Stratum: Clinical remission at Week 60 [Clinical remission, Non-remission]
Mucosal Healing at Week 60 [Mucosal healing, Non-healing]
- Visit: Weeks 2, 6, 10, 14, 22, 30, and 60
- Analysis methodology: The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase. When calculating geometric mean and geometric CV%, the analysis will be performed by excluding the data for which serum concentration of MLN0002 is 0. The adjudication results in the study site will be used as the score of findings on endoscopy.
- (1) Summary statistics, geometric mean, and geometric CV%

4.3 Serum Concentrations of MLN0002 by AVA and Neutralizing Antibody

- Analysis set: Subjects who underwent proper determination of serum concentrations of MLN0002 in the “full analysis set in the maintenance phase”
- Analysis variables: Serum concentrations of MLN0002
- Stratum: AVA in induction and maintenance phases [Negative, Positive]

	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody in induction and maintenance phases	[Negative, Positive]
Visit:	Weeks 2, 6, 10, 14, 22, 30, and 60	
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase. When calculating geometric mean and geometric CV%, the analysis will be performed by excluding the data for which serum concentration of MLN0002 is 0.	
	(1) Summary statistics, geometric mean, and geometric CV%	

4.4 Efficacy by Serum Concentration of MLN0002

Analysis set:	Subjects who underwent proper determination of serum concentrations of MLN0002 in the “full analysis set in the maintenance phase”	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
	Mucosal Healing at Week 60	[Mucosal healing, Non-healing]
Stratum:	Serum concentrations of MLN0002 at Week 2	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
	Serum concentrations of MLN0002 at Week 6	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
	Serum concentrations of MLN0002 at Week 10	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
	Serum concentrations of MLN0002 at Week 14	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
	Serum concentrations of MLN0002 at Week 22	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
	Serum concentrations of MLN0002 at Week 30	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
	Serum concentrations of MLN0002 at Week 60	$[0 \leq - < Q1, Q1 \leq - < \text{Median}, \text{Median} \leq - < Q3, Q3 \leq - \leq \text{Max}]$
Visit:	Week 60	
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy. Categories of stratum will be defined as 4 categories with the first quartile (Q1), median, and third quartile (Q3) of the obtained data in the MLN0002 group as boundaries.	

- (1) Frequency distributions, point estimates and 95% two-sided CI for the proportion

5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS

5.1 AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody in the “full analysis set in the maintenance phase”	
Analysis variables:	AVA	[Negative, Positive]
	AVA titer	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody	[Negative, Positive]
Visit:	Weeks 0, 10, 30, 60, and 16 weeks after the last dose of the study drug (AVA, AVA titer, neutralizing antibody)	
Analysis methodology:	The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase. The category of AVA titer will be set according to the observed AVA titer. The subjects who received the study drug in the open-label cohort will be excluded from the analysis at 16 weeks after the last dose. (1) Frequency distributions	

5.2 Efficacy by AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody in the “full analysis set in the maintenance phase”	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
	Mucosal healing at Week 60	[Mucosal healing, Non-healing]
Stratum:	AVA in the induction and maintenance phases	[Negative, Positive]
	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody in the induction and maintenance phases	[Negative, Positive]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase. Of note, the adjudication results in the study site will be used as the score of findings on endoscopy. (1) Frequency distributions	

5.3 AVA and Neutralizing Antibody by Concomitant Use of Immunomodulators

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing
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	antibody in the “full analysis set in the maintenance phase”	
Analysis variables:	AVA in the induction and maintenance phases	[Negative, Positive]
	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody in the induction and maintenance phases	[Negative, Positive]
Stratum:	Concomitant use of immunomodulators at Week 0	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids at Week 0	[Yes, No]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase.	
	The subjects who received the study drug in the open-label cohort will be excluded from the analysis at 16 weeks after the last dose.	
	(1) Frequency distributions	

6 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT

- Significance level: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided estimate)

History of Revision (version management)

Version	Date	Prepared/modified by	Comments
First Version	24 February 2017	PPD	Preparation of first version

[Appendix 1] Comparison Table for Changes

N/A

[Appendix 2] Definitions of Categories in Shift Table, MAV Criteria, and Criteria for Elevated Liver Enzyme

(1) Categories in Shift Table

The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

Test item	Categories
Albumin	≥LLN, <LLN to 3 g/dL, <3 g/dL to 2 g/dL, <2 g/dL to 1 g/dL, <1 g/dL
ALT(GPT)	≤ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
AST(GOT)	≤ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
Total bilirubin	≤ULN, >ULN to 1.5×ULN, >1.5×ULN to 3.0×ULN, >3.0×ULN to 10.0×ULN, >10.0×ULN
Creatinine	≤ULN, >ULN to 1.5×ULN, >1.5×ULN to 3.0×ULN, >3.0×ULN to 6.0×ULN, >6.0×ULN
ALP	≤ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
WBC	≥LLN, <LLN to 3000/μL, <3000/μL to 2000/μL, <2000/μL to 1000/μL, <1000/μL
WBC	≤ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Platelets	≥LLN, <LLN to 7.5×10 ⁴ /μL, <7.5×10 ⁴ /μL to 5.0×10 ⁴ /μL, <5.0×10 ⁴ /μL to 2.5×10 ⁴ /μL, <2.5×10 ⁴ /μL
Platelets	≤ULN, >ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN to 3.0×ULN, >3.0×ULN
Lymphocytes	≥800/μL, <800/μL to 500/μL, <500/μL to 200/μL, <200/μL
Lymphocytes (%)	≤ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Eosinophils (%)	≤ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Monocytes (%)	≤ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Basophils (%)	≤ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Hemoglobin	≥LLN, <LLN to 10 g/dL, <10 g/dL to 8 g/dL, <8 g/dL to 6.5 g/dL, <6.5 g/dL
Neutrophils	≥1500/μL, <1500/μL to 1000/μL, <1000/μL to 500/μL, <500/μL
Neutrophils (%)	≤ULN, >ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN to 3.0×ULN, >3.0×ULN

Missing data will not be included in any category.

(2) MAV Criteria

1) Hematology, Blood Biochemistry

For each test item, MAV will be determined according to the table below for evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) obtained from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort or from the day after the first dose of the study drug in the maintenance phase until 167 days* after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the open-label cohort. The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

* Day after the last dose of the study drug will be defined as Follow-up Day 1.

Test item	MAV Criteria	
	Lower criteria	Upper criteria
Hemoglobin (g/dL)	≤7	-
Lymphocytes (/μL)	<500	-
WBC (/μL)	<2000	-
Platelets (×10 ⁴ /μL)	<7.5	-
Neutrophils (/μL)	<1000	-
ALT(GPT) (U/L)	-	>3.0×ULN
AST(GOT) (U/L)	-	>3.0×ULN
Total bilirubin (mg/dL)	-	>2.0×ULN
Amylase (U/L)	-	>2.0×ULN

Classifying Subjects for the Overall Maintenance Phase

For each test item and subject, MAV will be determined according to the conditions [1] to [3] provided below.

- [1] A subject will be classified as those “with MAV” if he/she has at least one data that “meets the MAV Criteria” among the evaluable data obtained from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort or from the day after the first dose of the study drug in the maintenance phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the open-label cohort.

- [2] A subject will be classified as those “without MAV” if he/she does not meet condition [1] and has at least one data that does “not meet the MAV Criteria” among the evaluable data obtained from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort or from the day after the first dose of the study drug in the maintenance phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the open-label cohort.
- [3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of MAV for that item.

(3) Criteria for Elevated Liver Enzyme

For each test item, elevated liver enzyme will be determined according to the table below for evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) obtained from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort or from the day after the first dose of the study drug in the maintenance phase until 167 days* after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the open-label cohort. If there is more than one item that need to be considered for a criteria, test items measured on the same day will be used. The following abbreviations are used in the table below: LLN for lower limit of the normal range, ULN for upper limit of the normal range, ALT for alanine aminotransferase, AST for aspartate aminotransferase, Tbili for total bilirubin, and ALP for alkaline phosphatase.

* Day after the last dose of the study drug will be defined as Follow-up Day 1.

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
ALT > 3×ULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5×ULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8×ULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3×ULN with Tbili > 2×ULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3×ULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5×ULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8×ULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
AST > 3×ULN with Tbili > 2×ULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3×ULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5×ULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN
ALT or AST > 8×ULN	Either ALT or AST is greater than 8 times the ULN	Both ALT and AST are non-missing and less than or equal to 8 times the ULN
ALT or AST > 3×ULN with Tbili > 2×ULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALT and AST > 3×ULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN
ALT and AST > 5×ULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8×ULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3×ULN with Tbili > 2×ULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3×ULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3×ULN with ALT > 3×ULN	Both ALP and ALT are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3×ULN with AST > 3×ULN	Both ALP and AST are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

Classifying Subjects for the Overall Maintenance Phase

For each criteria and subject, “elevated liver enzyme” will be determined according to the conditions [1] to [3] provided below.

[1] A subject will be classified as those “with elevated liver enzyme” if he/she has at least one data

that “meets the criteria for elevated liver enzyme” among the evaluable data obtained from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort or from the day after the first dose of the study drug in the maintenance phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the open-label cohort.

- [2] A subject will be classified as those “without elevated liver enzyme” if he/she does not meet condition [1] and has at least one data that does “not meet the criteria for elevated liver enzyme” among the evaluable data obtained from the day after the first dose of the study drug in the maintenance phase until the day of the first dose of the study drug in the open-label cohort for subjects who received the study drug in the open-label cohort or from the day after the first dose of the study drug in the maintenance phase until 167 days after the last dose of the study drug (including Follow-up Day 167) for subjects who did not receive the study drug in the open-label cohort.
- [3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of elevated liver enzyme for that item.

STATISTICAL ANALYSIS PLAN (Open-Label Cohort)

Study Title : Phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and pharmacokinetics of intravenous MLN0002 (300 mg) infusion in induction and maintenance therapy in Japanese subjects with moderate or severe ulcerative colitis

Protocol No. : MLN0002/CCT-101

Sponsor : Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

PPD [Redacted] Takeda Pharmaceutical Company Limited

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Trial Statistician

PPD [Redacted] Takeda Pharmaceutical Company Limited

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Limited

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS3

HANDLING OF TIME WINDOW4

OTHER HANDLING10

1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS15

1.1 Disposition of Subjects15

 1.1.1 Study Information15

 1.1.2 Disposition of All Subjects Who Did Not Enter in the Open-label Cohort15

 1.1.3 Subject Eligibility15

 1.1.4 Number of Subjects Who Entered in the Open-label Cohort by Site.....15

 1.1.5 Disposition of Subjects16

 1.1.5.1 Disposition of Subjects16

 1.1.6 Study Drug Completion Status and Study Visit Completion Status17

 1.1.7 Protocol Deviations and Analysis Sets17

1.2 Demographic and Other Baseline Characteristics.....18

 1.2.1 Distribution of Baseline Demographics18

 1.2.2 Medical History, Concurrent Medical Conditions20

 1.2.3 Medication History, Concomitant Medications, Concomitant Therapies21

1.3 Measurement of Compliance Status for Treatment23

 1.3.1 Study Drug Exposure and Compliance23

2 EFFICACY ANALYSIS24

2.1 Other Endpoints and Analysis Methodology24

 2.1.1 Endpoints Related to Mayo Scores24

2.2 Statistical and Analytical Issues.....25

 2.2.1 Adjustments for Covariates.....25

 2.2.2 Handling of Dropouts or Missing Data.....25

 2.2.3 Interim Analyses and Data Monitoring.....25

 2.2.4 Multicenter Studies25

 2.2.5 Multiple Comparisons/Multiplicity.....25

 2.2.6 Use of an “Efficacy Subset of Subjects”25

 2.2.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority25

 2.2.8 Examination of Subgroups.....25

3 SAFETY ANALYSIS.....26

3.1 Treatment-Emergent Adverse Event.....26

 3.1.1 Overview of Treatment-Emergent Adverse Events26

 3.1.2 Displays of Treatment-Emergent Adverse Events27

3.2 Pretreatment Event.....29

3.2.1 Display of Pretreatment Event.....	29
3.3 Clinical Laboratory Evaluations and Other Safety Endpoints	29
3.3.1 Clinical Laboratory Evaluations	29
3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety	31
4 DISPLAY OF TREATMENT-EMERGENT ADVERSE EVENT (IN JAPANESE).....	32
4.1 Display of Treatment-Emergent Adverse Event (in Japanese)	32
5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS.....	33
5.1 AVA and Neutralizing Antibody	33
5.2 Efficacy by AVA and Neutralizing Antibody.....	33
5.3 AVA and Neutralizing Antibody by Concomitant Use of Immunomodulators.....	33
6 SAFETY ANALYSIS OF MLN0002 TREATMENT.....	35
6.1 Measurement of Compliance Status for Treatment	35
6.1.1 MLN0002 Exposure and Compliance in the Treatment Period.....	35
6.2 Treatment-Emergent Adverse Event.....	35
6.2.1 Overview of Treatment-Emergent Adverse Events	35
6.2.2 Displays of Treatment-Emergent Adverse Events.....	37
6.3 Display of Treatment-Emergent Adverse Event (in Japanese)	39
7 ANALYSIS OF FOLLOW-UP SURVEY AND PML CHECKLIST	39
7.1 Analysis of Follow-up Survey	39
7.2 Analysis of PML checklist.....	40
8 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT	40
History of Revision (version management)	41
[Appendix 1] Comparison Table for Changes	1
[Appendix 2] Definitions of Categories in Shift Table, MAV Criteria, and Criteria for Elevated Liver Enzyme	1

Since the study has different objectives in the induction phase, the maintenance phase and the open-label cohort, analyses will be conducted separately among these. Therefore, the “Statistical Analysis Plan” will be also prepared for the induction phase, maintenance phase, and open-label cohort respectively. This statistical analysis plan will describe the analytical plan in the open-label cohort.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

- Treatment-emergent adverse event (TEAE) in the open-label cohort: An adverse event that emerged during the open-label cohort.
- TEAEs emerged after treatment of MLN0002: TEAEs whose onset date is after the first dose of MLN0002
- Concomitant medication in the open-label cohort: All concomitant medications.
- Concomitant therapy in the open-label cohort: All concomitant therapies.
- Summary statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- MAV: An abbreviation for markedly abnormal value.
- Study Day: The day before the first dose of the study drug in the induction phase will be defined as Day -1 and the day of the first dose in the induction phase will be defined as Day 1.
- Study Day in the Open-label Cohort: The day before the first dose of the study drug in the open-label cohort will be defined as Day -1x and the day of the first dose in the open-label cohort will be defined as Day 1x.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1. There will be no distinction among the induction phase, maintenance phase, and open-label cohort for the day of the last dose of the study drug.
- Full analysis set in the open-label cohort: Subjects who received at least one dose of the study drug in the open-label cohort.
- Safety analysis set in the open-label cohort: Subjects who received at least one dose of the study drug in the open-label cohort.
- Determination of clinical response at Week 10: Determination of clinical response or non-response at Week 10 on the website of the registration center.
- Route to open-label cohort: Routes 1 to 8. See the following table for details of each route.

Name	Study Drug in the Induction Phase	Clinical Response at Week 10	Study Drug in the Maintenance Phase	Study Drug Completion Status in the Maintenance Phase	Features
Route 1	MLN0002	Clinical response	MLN0002	Completed	
Route 2	MLN0002	Clinical response	MLN0002	Discontinued	Reinduction to subjects with treatment failure in the maintenance phase (loss of response)
Route 3	MLN0002	Clinical response	Placebo	Completed	
Route 4	MLN0002	Clinical response	Placebo	Discontinued	Reinduction to subjects who achieved treatment success in the induction phase and were subsequently observed without any administration of the study drug but relapsed after that
Route 5	MLN0002	Non-response	-	-	Reinduction to subjects with treatment failure in the induction phase (inadequate response)
Route 6	Placebo	Clinical response	Placebo	Completed	
Route 7	Placebo	Clinical response	Placebo	Discontinued	
Route 8	Placebo	Non-response	-	-	

- Anti-vedolizumab antibody (AVA): Human anti-human antibody (HAHA) in the protocol will be described as AVA.

HANDLING OF TIME WINDOW

For each test, observation, and evaluation item, evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) will be handled according to the following rules.

The evaluable data within the acceptable window will be used. If more than one datum lies within the same acceptable window, the data whose test/observation/evaluation date is closest to the scheduled date will be used and, if there are two data equidistant to the scheduled date, the data obtained later will be used. The temporal distance from the scheduled date will be determined based

on the Study Day, Study Day in the Open-label Cohort, and Follow-up Day.

Partial Mayo score*¹, Mayo subscore (stool frequency, rectal bleeding, physician's global assessment)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 0	Study Day: 1	-28 to 1* ²	
Week 0x	Study Day in the Open-label Cohort: 1	Day after the first dose of the study drug in the induction phase to 1	
Week 2x	Study Day in the Open-label Cohort: 15	2 to 28	
Week 6x	Study Day in the Open-label Cohort: 43	29 to 56	
Week 10x	Study Day in the Open-label Cohort: 71	57 to 84	
Week 14x	Study Day in the Open-label Cohort: 99	85 to 112	
Week 18x	Study Day in the Open-label Cohort: 127	113 to 140	
Week 22x	Study Day in the Open-label Cohort: 155	141 to 168	
Week 26x	Study Day in the Open-label Cohort: 183	169 to 196	
Week 30x	Study Day in the Open-label Cohort: 211	197 to 224	
Week 34x	Study Day in the Open-label Cohort: 239	225 to 252	
Week 38x	Study Day in the Open-label Cohort: 267	253 to 280	
Week 42x	Study Day in the Open-label Cohort: 295	281 to 308	
Week 46x	Study Day in the Open-label Cohort: 323	309 to 336	
Week 50x	Study Day in the Open-label Cohort: 351	337 to 364	
Week 54x	Study Day in the Open-label Cohort: 379	365 to 392	
Week 58x	Study Day in the Open-label Cohort: 407	393 to 420	
Week 62x	Study Day in the Open-label Cohort: 435	421 to 448	
Week 66x	Study Day in the Open-label Cohort: 463	449 to 476	
Week 70x	Study Day in the Open-label Cohort: 491	477 to 504	
Week 74x	Study Day in the Open-label Cohort: 519	505 to 532	
Week 78x	Study Day in the Open-label Cohort: 547	533 to 560	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 82x	Study Day in the Open-label Cohort: 575	561 to 588	
Week 86x	Study Day in the Open-label Cohort: 603	589 to 616	
Week 90x	Study Day in the Open-label Cohort: 631	617 to 644	
Week 94x	Study Day in the Open-label Cohort: 659	645 to 686	
Week 94x (LOCF)* ³	Study Day in the Open-label Cohort:	2 to	

*¹ Clinical response based on partial Mayo score will be determined based on partial Mayo scores.

*² At Week 0, the acceptable window will be defined based on the Study Day, not on the Study Day in the Open-label Cohort.

*³ For Week 94x (LOCF), the latest data during the period from the day after the first dose of the study drug in the open-label cohort onwards will be used.

Laboratory tests (hematology, blood biochemistry, inflammatory markers)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 0	Study Day: 1	-28 to 1* ¹	
Week 0x	Study Day in the Open-label Cohort: 1	Day after the first dose of the study drug in the induction phase to 1	
Week 2x	Study Day in the Open-label Cohort: 15	2 to 28	
Week 6x	Study Day in the Open-label Cohort: 43	29 to 56	
Week 14x	Study Day in the Open-label Cohort: 99	71 to 126	
Week 22x	Study Day in the Open-label Cohort: 155	127 to 182	
Week 30x	Study Day in the Open-label Cohort: 211	183 to 238	
Week 38x	Study Day in the Open-label Cohort: 267	239 to 294	
Week 46x	Study Day in the Open-label Cohort: 323	295 to 350	
Week 54x	Study Day in the Open-label Cohort: 379	351 to 406	
Week 62x	Study Day in the Open-label Cohort: 435	407 to 462	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 70x	Study Day in the Open-label Cohort: 491	463 to 518	
Week 78x	Study Day in the Open-label Cohort: 547	519 to 574	
Week 86x	Study Day in the Open-label Cohort: 603	575 to 630	
Week 94x	Study Day in the Open-label Cohort: 659	631 to 686	
16 weeks after the last dose of the study drug* ²	Follow-up Day: 112		56 to 167

*¹ At Week 0, the acceptable window will be defined based on the Study Day, not on the Study Day in the Open-label Cohort.

*² Not applied to laboratory test (inflammatory markers).

Laboratory test (urinalysis), 12-lead ECG

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 0	Study Day: 1	-28 to 1* ¹	
Week 0x	Study Day in the Open-label Cohort: 1	Day after the first dose of the study drug in the induction phase to 1	
Week 94x	Study Day in the Open-label Cohort: 659	2 to 686	
16 weeks after the last dose	Follow-up Day: 112		56 to 167

*¹ At Week 0, the acceptable window will be defined based on the Study Day.

Vital signs, body weight

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 0	Study Day: 1	-28 to 1* ¹	
Week 0x	Study Day in the Open-label Cohort: 1	Day after the first dose of the study drug in the induction phase to 1	
Week 2x	Study Day in the Open-label Cohort: 15	2 to 28	
Week 6x	Study Day in the Open-label Cohort: 43	29 to 56	
Week 10x	Study Day in the Open-label Cohort: 71	57 to 84	
Week 14x	Study Day in the Open-label Cohort: 99	85 to 112	
Week 18x	Study Day in the Open-label Cohort: 127	113 to 140	
Week 22x	Study Day in the Open-label Cohort: 155	141 to 168	
Week 26x	Study Day in the Open-label Cohort: 183	169 to 196	
Week 30x	Study Day in the Open-label Cohort: 211	197 to 224	
Week 34x	Study Day in the Open-label Cohort: 239	225 to 252	
Week 38x	Study Day in the Open-label Cohort: 267	253 to 280	
Week 42x	Study Day in the Open-label Cohort: 295	281 to 308	
Week 46x	Study Day in the Open-label Cohort: 323	309 to 336	
Week 50x	Study Day in the Open-label Cohort: 351	337 to 364	
Week 54x	Study Day in the Open-label Cohort: 379	365 to 392	
Week 58x	Study Day in the Open-label Cohort: 407	393 to 420	
Week 62x	Study Day in the Open-label Cohort: 435	421 to 448	
Week 66x	Study Day in the Open-label Cohort: 463	449 to 476	
Week 70x	Study Day in the Open-label Cohort: 491	477 to 504	
Week 74x	Study Day in the Open-label Cohort: 519	505 to 532	
Week 78x	Study Day in the Open-label Cohort: 547	533 to 560	
Week 82x	Study Day in the Open-label Cohort: 575	561 to 588	
Week 86x	Study Day in the Open-label Cohort: 603	589 to 616	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 90x	Study Day in the Open-label Cohort: 631	617 to 644	
Week 94x	Study Day in the Open-label Cohort: 659	645 to 686	
16 weeks after the last dose	Follow-up Day: 112		56 to 167

*¹ At Week 0, the acceptable window will be defined based on the Study Day, not on the Study Day in the Open-label Cohort.

AVA, neutralizing antibody

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 0	Study Day: 1	-28 to 1* ¹	
Week 0x	Study Day in the Open-label Cohort: 1	Day after the first dose of the study drug in the induction phase to 1	
Week 10x	Study Day in the Open-label Cohort: 71	2 to 84	
Week 30x	Study Day in the Open-label Cohort: 211	85 to 322	
Week 62x	Study Day in the Open-label Cohort: 435	323 to 546	
Week 94x	Study Day in the Open-label Cohort: 659	547 to 686	
16 weeks after the last dose	Follow-up Day: 112		56 to 167

*¹ At Week 0, the acceptable window will be defined based on the Study Day, not on the Study Day in the Open-label Cohort.

Follow-up interview

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
6 months after the last dose	Follow-up Day: 182		1 to 273

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
12 months after the last dose	Follow-up Day: 365		274 to 455
18 months after the last dose	Follow-up Day: 547		456 to 638
24 months after the last dose	Follow-up Day: 730		639 to 820

OTHER HANDLING

In principle, if any variable value used for calculation or adjudication is missing, the result of the calculation or adjudication will be handled as missing. If other handling of missing data is described, follow that handling.

- Duration of study drug exposure in the open-label cohort (day): Date of the last dose of the study drug in the open-label cohort – Date of the first dose of the study drug in the open-label cohort + 1
- Duration on study after the first dose of the study drug in the open-label cohort (day): Date of last visit or contact – Date of the first dose of the study drug in the open-label cohort + 1”
- Duration of MLN0002 exposure (day): Date of the last dose of MLN0002 – Date of the first dose of MLN0002 + 1
- Duration on study after the first dose of MLN0002 (day): Date of last visit or contact – Date of the first dose of MLN0002 + 1
- BMI (kg/m²) = Weight (kg) / (Height [cm]/100)² (round off to the first decimal place)
- Duration of UC (year): (Date of informed consent [year and month] – Date of UC diagnosis [year and month]) / 12 (round off to the first decimal place)
 - Only year and month for date of informed consent will be used.
 - The unit for “Date of informed consent (year and month) – Date of UC diagnosis (year and month)” will be “months.”
 - If the year of UC diagnosis is unknown, the duration of UC will be handled as “Missing.” If only the month of UC diagnosis is unknown, the duration of UC will be calculated by setting the month of UC diagnosis as January.
- Prior corticosteroids failure: If corticosteroids resistance, dependence, or intolerance is “Yes,” prior corticosteroids failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Classification 1 of prior corticosteroids failure: Subjects for whom prior corticosteroid failure is “Yes” are classified as follows:
 - Subjects for whom corticosteroid resistance is “Yes” are classified as “Resistance.”

- Among subjects for whom corticosteroids resistance is not “Yes,” subjects for whom corticosteroid dependence is “Yes” are classified as “Dependence.”
- Among subjects for whom corticosteroids resistance is not “Yes” as well as corticosteroid dependence not being “Yes,” subjects for whom corticosteroid intolerance is “Yes” are classified as “Intolerance.”
- Classification 2 of prior corticosteroids failure: Subjects for whom prior corticosteroid failure is “Yes” are classified as follows:
 - Subjects for whom corticosteroid resistance is “Yes” or corticosteroid dependence is “Yes” are classified as “Refractory.”
 - Among subjects for whom corticosteroids resistance is not “Yes” as well as corticosteroid dependence not being “Yes,” subjects for whom corticosteroid intolerance is “Yes” are classified as “Intolerance.”
- Prior immunomodulators failure: If either of immunomodulator refractory or intolerance is “Yes,” prior immunomodulators failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Classification of prior immunomodulators failure: Subjects for whom prior immunomodulators failure is “Yes” are classified as follows:
 - Subjects for whom immunomodulator refractory is “Yes” are classified as “Refractory.”
 - Among the subjects for whom immunomodulator refractory are not “Yes,” subjects for whom immunomodulatory intolerance is “Yes” are classified as “Intolerance.”
- Prior TNF α antagonist failure: If inadequate response, loss of response, or intolerance to the TNF α antagonist is “Yes,” prior TNF α antagonist failure will be defined as “Yes.” Any response other than the above will be defined as “No.”
- Number of drugs of TNF α antagonist failure: Among the drugs entered to prior treatment failure (TNF α antagonist) for UC, subjects whose Who Drug is coded with 1 type of drug with Preferred Name are classified as “Treatment failure with 1 drug.” Similarly, subjects who are coded with 2 types of drugs are classified as “Treatment failure with 2 drugs” and subjects who are coded with 3 types of drugs as “Treatment failure with 3 drugs.” Subjects who are not coded with any drug in the prior treatment failure (TNF α antagonist) for UC are classified as “None.”
- Classification of prior TNF α antagonist failure: Subjects for whom TNF α antagonist failure is “Yes” are classified as follows:
 - Subjects for whom TNF α antagonist inadequate response is “Yes” are classified as “Inadequate response.”
 - Among subjects for whom TNF α antagonist inadequate response is not “Yes,” subjects for whom TNF α antagonist loss of response is “Yes” are classified as “Loss of response.”
 - Among subjects for whom TNF α antagonist inadequate response is not “Yes” as well as TNF α antagonist loss of response not being “Yes,” subjects for whom TNF α antagonist

intolerance is “Yes” are classified as “Intolerance.”

- Prior immunomodulators failure (excluding prior TNF α antagonist failure): If prior TNF α antagonist failure is “No” and prior immunomodulators failure is “Yes,” prior immunomodulators failure (excluding prior TNF α antagonist failure) will be defined as “Yes.” All others will be defined as “No.”
- Prior corticosteroid failure only: If prior TNF α antagonist failure is “No,” prior immunomodulators failure is “No,” and prior corticosteroids failure is “Yes,” prior corticosteroid failure only will be defined as “Yes.” All others will be defined as “No.”
- Prior immunomodulators and TNF α antagonist failure: If prior immunomodulators failure is “Yes” and prior TNF α antagonist failure is “Yes,” prior immunomodulators and TNF α antagonist failure will be defined as “Yes.” All others will be defined as “No.”
- Completion of the study drug infusion: If the infusion of the study drug is “Completed” or dose of the study drug is ≥ 79 mL (percentage of dose against prepared study drug of 105 mL is $\geq 75\%$), the study drug infusion will be defined as “Completed.” All others will be defined as “Incompleted.”

Mayo score will be handled as follows:

- Partial Mayo score: Sum of subscores for stool frequency, rectal bleeding, and physician’s global assessment.
 - The partial Mayo score will be calculated using subscores on the same day of measurement. The day of evaluation for stool frequency and rectal bleeding will be the same as the day of evaluation for physician’s global assessment.
 - If any of the subscores for stool frequency, rectal bleeding, and physician’s global assessment used for calculation of the partial Mayo score are missing, the partial Mayo score will be handled as missing.
- Clinical response based on partial Mayo score: If the following 2 conditions are fulfilled, subjects will be classified as “Clinical response based on partial Mayo score.” All others will be classified as “Non-response based on partial Mayo score.” However, if any of the scores used for adjudication is missing, it will be handled as missing. Then, if the adjudication result at that visit is missing (including cases with no data due to study discontinuation) after processing “HANDLING OF TIME WINDOW,” subjects will be classified as “Non-response based on partial Mayo score.”
 - Decrease of the partial Mayo score by ≥ 2 points and by $\geq 25\%$ from baseline (Week 0)
 - Decrease of the subscore of rectal bleeding by ≥ 1 point from baseline (Week 0) or ≤ 1 in the subscore of rectal bleeding

A prior TNF α antagonist use, concomitant use of immunomodulators at Week 0, and concomitant

use of oral corticosteroids at Week 0 will be defined as follows:

- Prior TNF α antagonist use: Subjects coded with at least 1 drug of Preferred Name of Who Drug in the following table for medication history will be classified as “Yes.” All others will be classified as “No.”

Preferred Name
Infliximab
Adalimumab
Golimumab

- Concomitant use of immunomodulators at Week 0: Subjects who received any concomitant medication (for treatment of UC) which is classified as “immunomodulators” in the concomitant medication (for treatment of UC) which was started before the first dose of the study drug in the induction phase and continued in the induction phase will be classified as “Yes.” All others will be classified as “No.”
 - Any concomitant medication (for treatment of UC) which was started after the first dose of the study drug in the induction phase is not subject to this handling.
- Concomitant use of oral corticosteroids at Week 0: Subjects who received any concomitant medication (for treatment of UC) which is classified as “corticosteroids” and whose route of administration is “oral” in the concomitant medication (for treatment of UC) which was started before the first dose of the study drug in the induction phase and continued in the induction phase will be classified as “Yes.” All others will be classified as “No.”
 - Any concomitant medication (for treatment of UC) which was started after the first dose of the study drug in the induction phase is not subject to this handling.

Negative or positive (persistently positive, transiently positive) status of AVA will be determined as follows:

- Persistently positive
 - “Subjects who were determined to be AVA-positive in at least 2 consecutive samples sorted by date of blood collection after the day of the first dose of the study drug in the induction phase” or “subjects who were determined to be AVA-positive in the latest sample collected after the day of the first dose of the study drug in the induction phase” will be classified as persistently positive.
- Transient positive
 - Subjects who do not correspond to “subjects who were determined to be AVA-positive in at least 2 consecutive samples sorted by date of blood collection after the day of the first

dose of the study drug in the induction phase,” and determined to be AVA-positive in at least one sample collected after the day of the first dose of the study drug in the induction phase will be classified as transiently positive.

Negative or positive status of the neutralizing antibody will be determined as follows:

- “Positive” if the neutralizing antibody is positive for AVA and neutralizing antibody with the same VISIT in each subject. “Negative” if the neutralizing antibody is negative or AVA is negative. Neutralizing antibody will be handled as missing if it does not correspond to any of the above.

“AVA in the induction phase, maintenance phase, and open-label cohort” and “neutralizing antibody in the induction phase, maintenance phase, and open-label cohort” will be defined as follows:

- AVA in the induction phase, maintenance phase, and open-label cohort
 - Subjects who were determined to be AVA-positive at any visit after the day of the first dose of the study drug in the induction phase, in the maintenance phase, or in the open-label cohort will be classified as “AVA-positive.” Subjects who were determined to be AVA-negative at all visits (except for those with missing values) after the day of the first dose of the study drug in the induction phase, in the maintenance phase, and in the open-label cohort will be classified as “AVA-negative.” Subjects whose AVA values are missing at all visits after the day of the first dose of the study drug in the induction phase, in the maintenance phase, and in the open-label cohort will be classified as missing.
- Neutralizing antibody in the induction phase, maintenance phase, and open-label cohort
 - Subjects who were determined to be positive for neutralizing antibodies at any visit after the day of the first dose of the study drug in the induction phase, in the maintenance phase, or in the open-label cohort will be classified as “Positive for neutralizing antibodies.” Subjects who were determined to be negative for neutralizing antibodies at all visits (except for those with missing values) after the day of the first dose of the study drug in the induction phase, in the maintenance phase, and in the open-label cohort will be classified as “Negative for neutralizing antibodies.” Subjects whose neutralizing antibody values are missing at all visits after the day of the first dose of the study drug in the induction phase, in the maintenance phase, and in the open-label cohort will be classified as missing.

Lymphocytes and neutrophils will be calculated with the following formula:

- $\text{Lymphocytes} = \text{WBC} \times \text{lymphocytes (\%)}$
- $\text{Neutrophils} = \text{WBC} \times \text{neutrophils (\%)}$

1 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS

1.1 Disposition of Subjects

1.1.1 Study Information

Analysis set: All subjects who signed the informed consent form

Analysis variables: Date first subject signed the informed consent form
Date of the last visit or contact in the open-label cohort, whichever comes latest
MedDRA version
WHO Drug version
SAS version used for creating the datasets

Analysis methodology: The following analysis will be performed for the above analysis variables.
(1) Display of the analysis variables

1.1.2 Disposition of All Subjects Who Did Not Enter in the Open-label Cohort

Analysis set: All subjects who received at least one dose of the study drug in the induction or maintenance phases and did not enter in the open-label cohort

Analysis variables: Categories in parenthesis [] (hereinafter the same)
Age (years) [Min≤ - ≤34, 35≤ - ≤Max]
[Min≤ - ≤64, 65≤ - ≤Max]
Gender [Male, Female]

Analysis methodology: The following analysis will be performed for the above analysis variables.
(1) Frequency distributions for categorical variables and summary statistics for continuous variables

1.1.3 Subject Eligibility

Analysis set: Subjects who received at least one dose of the study drug in the induction or maintenance phases

Analysis variables: Eligibility for entering into the open-label cohort [Eligible, Not eligible]

Analysis methodology: The following analysis will be performed for the above analysis variables.
(1) Frequency distributions

1.1.4 Number of Subjects Who Entered in the Open-label Cohort by Site

Analysis set: All subjects who entered in the open-label cohort

Analysis variables: Eligibility for entering into the open-label cohort [Eligible]

Stratum:	Study site	[Site numbers will be used as categories]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum.	
	(1) Frequency distributions	

1.1.5 Disposition of Subjects

1.1.5.1 Disposition of Subjects

Analysis set:	All subjects who entered in the open-label cohort	
Analysis variables:	Study drug administration status in the open-label cohort	[Not treated]
	Reason for not being treated	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study drug completion status in the open-label cohort	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study visit completion status in the open-label cohort	[Completed, Incompleted]
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Analysis methodology:	The following analysis will be performed for the above analysis variables. When calculating percentages of the reasons for not being treated, the number of subjects who did not receive the study drug in the open-label cohort will be used as the denominator. When calculating percentages of the reasons for not being completed, the number of subjects who did not completed the study drug/study visit in the open-label cohort will be used as the denominator.	

(1) Frequency distributions

1.1.6 Study Drug Completion Status and Study Visit Completion Status

Analysis set:	All subjects who entered in the open-label cohort	
Analysis variables:	Study drug completion status	[Completed, Incompleted]
	in the open-label cohort	
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
	Study visit completion status	[Completed, Incompleted]
	in the open-label cohort	
	Reason for not being completed	[Pretreatment event/Adverse event, Major protocol deviation, Lost to follow-up, Voluntary withdrawal, Study termination, Pregnancy, Lack of efficacy, Other]
Categories:	Duration of study drug exposure in the open-label cohort (days)	[0, 1≤ - ≤42, 43≤ - ≤98, 99≤ - ≤210, 211≤ - ≤322, 323≤ - ≤434, 435≤ - ≤546, 547≤ - ≤Max]
	Duration on study after the first dose of the study drug in the open-label cohort (days)	[0, 1≤ - ≤42, 43≤ - ≤98, 99≤ - ≤210, 211≤ - ≤322, 323≤ - ≤434, 435≤ - ≤546, 547≤ - ≤Max]
Analysis methodology:	The following analysis will be performed for the above analysis variables. Frequency distributions will be provided for study drug completion status in the open-label cohort in the analysis of (1). Frequency distributions will be provided for study visit completion status in the open-label cohort in the analysis of (2).	
	(1)	Frequency distribution by duration of study drug exposure in the open-label cohort
	(2)	Frequency distribution by duration on study after the first dose of the study drug in the open-label cohort

1.1.7 Protocol Deviations and Analysis Sets

1.1.7.1 Protocol Deviations in the Open-label Cohort

Analysis set: All subjects who entered in the open-label cohort

Analysis variables:	Protocol deviations in the open-label cohort	[Major GCP violations, Deviations of protocol entry criteria, Deviations of discontinuation criteria, Deviations related to treatment procedure or dose, Deviations concerning excluded medication or therapy, Deviations to avoid emergency risk, Other]
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Analysis methodology:	<p>The following analysis will be performed for the above analysis variables.</p> <p>Frequency distribution of subjects with protocol deviations in the open-label cohort will be provided for above each deviation category. A subject who has several deviations that can be classified into the same category will be counted once in each appropriate category (overlapped counting).</p> <p>(1) Frequency distributions</p>	
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1.1.7.2 Analysis Sets of All Subjects Who Entered in the Open-label Cohort

Analysis set:	All subjects who entered in the open-label cohort	
Analysis variables:	Handling of subjects and subject data in the open-label cohort in analysis sets	[Categories are based on the specifications in “Handling Rules for Analysis Data”]
	Inclusion/Exclusion of analysis sets	
	Full analysis set in the open-label cohort	[Included]
	Safety analysis set in the open-label cohort	[Included]
Analysis methodology:	<p>The following analyses of (1) to (3) will be performed for the above analysis variables.</p> <p>A subject who corresponds to several categories in (1) and (2) will be counted once in each appropriate category (overlapped counting).</p> <p>(1) Frequency distributions concerning the handling of subjects in the open-label cohort in each analysis set</p> <p>(2) Frequency distributions concerning the handling of subject data in the open-label cohort in each analysis set</p> <p>(3) Frequency distributions concerning the number of subjects included in each analysis set</p>	

1.2 Demographic and Other Baseline Characteristics

1.2.1 Distribution of Baseline Demographics

Analysis set:	All subjects who entered in the open-label cohort
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Analysis variables:	Age (years)	[Min≤ - ≤34, 35≤ - ≤Max]
		[Min≤ - ≤64, 65≤ - ≤Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg) at Week 0	[Min≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
	BMI (kg/m ²) at Week 0	[Min≤ - ≤18.4, 18.5≤ - ≤24.9, 25.0≤ - ≤Max]
	Smoking classification	[Never smoked, Current smoker, Ex-smoker]
	Duration of UC (years)	[Min≤ - <1, 1≤ - <3, 3≤ - <7, 7≤ - ≤Max, Missing]
	Prior corticosteroids failure	[Yes, No]
	Classification 1 of prior corticosteroids failure	[Resistance, Dependence, Intolerance]
	Classification 2 of prior corticosteroids failure	[Refractory, Intolerance]
	Prior immunomodulators failure	[Yes, No]
	Classification of prior immunomodulators failure	[Refractory, Intolerance]
	Prior TNF α antagonist failure	[Yes, No]
	Number of drugs of TNF α antagonist failure	[1 drug, 2 drugs, 3 drugs, None]
	Classification of prior TNF α antagonist failure	[Inadequate response, Loss of response, Intolerance]
	Worst prior treatment failures	[Prior TNF α antagonist failure, Prior immunomodulators failure but not TNF α antagonist failure, Prior corticosteroid failure only]
	Prior immunomodulators and TNF α antagonist failure	[Yes, No]
	Prior TNF α antagonist use	[Yes, No]
	Infliximab	[Yes, No]
	Adalimumab	[Yes, No]
	Golimumab	[Yes, No]
	Concomitant use of 5-ASA at Week 0	[Yes, No]
	Concomitant use of	[Yes, No]

	immunomodulators at Week 0	
	Concomitant use of oral corticosteroids at Week 0	[Yes, No]
	No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0	[Yes, No]
	Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at Week 0 (concomitant use of oral corticosteroids only)	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0	[Yes, No]
	Complete Mayo score at Week 0	[0 ≤ - ≤5, 6 ≤ - ≤8, 9 ≤ - ≤12]
	Disease localization	[Total colitis, Left-sided colitis]
	Concurrent extraintestinal manifestations	[Yes, No]
	Number of MLN0002 infusion in the induction and maintenance phases	[1, 2, 3, 4, 5, 6, 7, 8, 9]
	Route to the open-label cohort	[Route 1, Route 2, Route 3, Route 4, Route 5, Route 6, Route 7, Route 8]
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Frequency distributions for categorical variables and summary statistics for continuous variables	

1.2.2 Medical History, Concurrent Medical Conditions

Analysis set:	Safety analysis set in the open-label cohort
Analysis variables:	Medical history Concurrent medical conditions (concurrent extraintestinal manifestations of

UC)

Concurrent medical conditions (other than concurrent extraintestinal manifestations of UC)

Analysis methodology: The following analysis will be performed for the above analysis variables. The analysis variables will be coded by use of MedDRA and will be summarized based on the SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

- (1) Frequency distributions for medical history (by SOC and PT)
- (2) Frequency distributions for concurrent medical conditions (concurrent extraintestinal manifestations of UC) (by SOC and PT)
- (3) Frequency distributions for concurrent medical conditions (other than concurrent extraintestinal manifestations of UC) (by SOC and PT)

The frequency distributions will be provided according to the rules below:
[Number of subjects]

A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC.
A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

1.2.3 Medication History, Concomitant Medications, Concomitant Therapies

Analysis set:	Safety analysis set in the open-label cohort	
Analysis variables:	Medication history	
	Concomitant medications (for treatment of UC) in the open-label cohort	
	Classification of concomitant medications (for treatment of UC) in the open-label cohort	[5-ASA, Corticosteroids, Immunomodulators, Other]
	Concomitant medications (for treatment of UC) in the open-label cohort that fall under the category of rescue treatments	
	Classification of concomitant medications (for treatment of UC) in the open-label cohort that fall under the category of rescue treatments	[5-ASA, Corticosteroids, Immunomodulators, Other]
	Concomitant medications (for other than treatment of UC) in the open-label cohort	
	Concomitant therapies in the open-label cohort	[Yes, No]
	Concomitant therapies in the open-label cohort	[Yes, No]

that fall under the category of rescue treatments

Analysis methodology: The following analysis will be performed for the above analysis variables. Medication history, concomitant medications (for treatment of UC) in the open-label cohort, concomitant medications (for treatment of UC) in the open-label cohort that fall under the category of rescue treatments, and concomitant medications (for other than treatment of UC) in the open-label cohort will be coded by use of WHO Drug and summarized based on Preferred Name, which will be sorted in decreasing frequency. A subject who has been administered several medications with the same Preferred Name will be counted only once for that Preferred Name.

- (1) Frequency distributions for medication history
- (2) Frequency distributions for concomitant medications (for treatment of UC) in the open-label cohort that were ongoing at the first dose of the study drug in the open-label cohort and continued in the open-label cohort, and concomitant medications (for treatment of UC) in the open-label cohort that started after the first dose of the study drug in the open-label cohort by category
- (3) Frequency distributions for concomitant medications (for treatment of UC) in the open-label cohort that fall under the category of rescue treatments, were ongoing at the first dose of the study drug in the open-label cohort and continued in the open-label cohort, and concomitant medications (for treatment of UC) in the open-label cohort that fall under the category of rescue treatments and started after the first dose of the study drug in the open-label cohort by category
- (4) Frequency distributions for concomitant medications (for other than treatment of UC) in the open-label cohort that were ongoing at the first dose of the study drug in the open-label cohort and continued in the open-label cohort, and concomitant medications (for other than treatment of UC) in the open-label cohort that started after the first dose of the study drug in the open-label cohort
- (5) Frequency distributions for presence or absence of concomitant therapies in the open-label cohort that were ongoing at the first dose of the study drug in the open-label cohort and continued in the open-label cohort, and concomitant therapies in the open-label cohort that started after the first dose of the study drug in the open-label cohort
- (6) Frequency distributions for presence or absence of concomitant therapies in the open-label cohort that fall under the category of rescue treatments, were ongoing at the first dose of the study drug in the open-label cohort and continued in the open-label cohort, and

concomitant therapies in the open-label cohort that fall under the category of rescue treatments and started after the first dose of the study drug in the open-label cohort

1.3 Measurement of Compliance Status for Treatment

1.3.1 Study Drug Exposure and Compliance

Analysis set:	Safety analysis set in the open-label cohort	
Analysis variables:	Duration of study drug exposure in the open-label cohort (days)	[1≤ - ≤42, 43≤ - ≤98, 99≤ - ≤210, 211≤ - ≤322, 323≤ - ≤434, 435≤ - ≤546, 547≤ - ≤Max]
	Duration on study after the first dose of the study drug in the open-label cohort (days)	[1≤ - ≤42, 43≤ - ≤98, 99≤ - ≤210, 211≤ - ≤322, 323≤ - ≤434, 435≤ - ≤546, 547≤ - ≤Max]
	Number of study drug infusion in the open-label cohort (times)	[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]
	Number of completed infusions of the study drug in the open-label cohort (times)	[0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]
	Number of completed or incompletd infusions in total infusions in the open-label cohort	[Completed, Incompleted]
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Frequency distributions for categorical variables and summary statistics for continuous variables	
	In the frequency distributions for number of completed or incompletd infusions in total infusions in the open-label cohort, the sum of the number of completed infusions in the open-label cohort will be counted as frequency for “Completed,” and the sum of the number of incompletd infusions will be counted as frequency for “Incompleted.” When calculating percentage, the sum of the number of completed infusions and the number of incompletd infusions (i.e., number of total infusions in the open-label cohort) will be used as the denominator.	

2 EFFICACY ANALYSIS

2.1 Other Endpoints and Analysis Methodology

2.1.1 Endpoints Related to Mayo Scores

Analysis set:	Full analysis set in the open-label cohort
Analysis	Partial Mayo score
variables:	Partial Mayo score change from baseline (Week 0) Clinical response based on partial Mayo score [Clinical response, Non-response] Each Mayo subscore (stool frequency, rectal bleeding, and physician's global assessment) [0, 1, 2, 3] Change in each Mayo subscore (stool frequency, rectal bleeding, and physician's global assessment) from baseline (Week 0)
Visit:	Weeks 0, 0x, 2x, 6x, 10x, 14x, 18x, 22x, 26x, 30x, 34x, 38x, 42x, 46x, 50x, 54x, 58x, 62x, 66x, 70x, 74x, 78x, 82x, 86x, 90x, 94x, and 94x (LOCF) (partial Mayo score, each Mayo subscore [stool frequency, rectal bleeding, and physician's global assessment]) Weeks 0x, 2x, 6x, 10x, 14x, 18x, 22x, 26x, 30x, 34x, 38x, 42x, 46x, 50x, 54x, 58x, 62x, 66x, 70x, 74x, 78x, 82x, 86x, 90x, 94x, and 94x (LOCF) (partial Mayo score change from baseline [Week 0], clinical response based on partial Mayo score, change in each Mayo subscore [stool frequency, rectal bleeding, and physician's global assessment] from baseline [Week 0])
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Summary statistics and 95% two-sided CI of the mean will be calculated for partial Mayo scores at each visit. (2) Summary statistics and 95% two-sided CI of the mean will be calculated for partial Mayo score changes from baseline (Week 0) at each visit. (3) Frequency distributions will be provided for the clinical response based on partial Mayo score at each visit along with the point estimate and 95% two-sided CI for the proportion. (4) Summary statistics and 95% two-sided CI of the mean will be calculated for each Mayo subscore (stool frequency, rectal bleeding, and physician's global assessment) at each visit. (5) Summary statistics and 95% two-sided CI of the mean will be calculated for change in each Mayo subscore (stool frequency, rectal bleeding, and physician's global assessment) from baseline (Week 0) at each visit. (6) Frequency distributions will be provided for each Mayo subscore (stool frequency, rectal bleeding, and physician's global assessment) at each visit.

2.2 Statistical and Analytical Issues

2.2.1 Adjustments for Covariates

Not applicable in the open-label cohort.

2.2.2 Handling of Dropouts or Missing Data

The efficacy endpoints of clinical response, clinical remission, or mucosal healing will be considered as non-response, non-remission, or non-healing, when adjudication for these endpoints is missing at that visit.

For other endpoints, missing test results and ineligible data according to the “Handling Rules for Analysis Data” or the SAP will be excluded from statistical analyses and estimations.

Values below the limit of quantification will be handled as 0.

2.2.3 Interim Analyses and Data Monitoring

No interim analyses will be performed for the induction and maintenance phases.

In the open-label cohort, the data for the marketing application as fixed on the cut-off date will be analyzed after fixing the data of all subjects fixed on the cut-off date for the marketing application. Continuation/termination of the study, and change in clinical trial plan, and so on will not be judged based on the analysis.

2.2.4 Multicenter Studies

Since a single-arm design is employed in the open-label cohort of this study, interactions between treatment and study site will not be investigated.

2.2.5 Multiple Comparisons/Multiplicity

Not applicable in the open-label cohort.

2.2.6 Use of an “Efficacy Subset of Subjects”

Not applicable in the open-label cohort.

2.2.7 Active-Control Studies Intended to Show Equivalence or Non-inferiority

Not applicable.

2.2.8 Examination of Subgroups

Not applicable in the open-label cohort.

3 SAFETY ANALYSIS

3.1 Treatment-Emergent Adverse Event

3.1.1 Overview of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set in the open-label cohort	
Analysis variables:	TEAEs in the open-label cohort	
Categories:	Causality	[Related, Not related]
	Intensity	[Mild, Moderate, Severe]
Analysis methodology:	The following summaries will be provided for the above analysis variables.	
	(1)	Overview of TEAEs in the open-label cohort
	1)	All TEAEs in the open-label cohort (number of events, number and percentage of subjects)
	2)	Causal relationship between all TEAEs in the open-label cohort and study drug (number of events, number and percentage of subjects)
	3)	Intensity of all TEAEs in the open-label cohort (number of events, number and percentage of subjects)
	4)	TEAEs in the open-label cohort leading to study drug discontinuation (number of events, number and percentage of subjects)
	5)	Serious TEAEs in the open-label cohort (number of events, number and percentage of subjects)
	6)	Causal relationship between serious TEAEs in the open-label cohort and study drug (number of events, number and percentage of subjects)
	7)	Serious TEAEs in the open-label cohort leading to study drug discontinuation (number of events, number and percentage of subjects)
	8)	TEAEs in the open-label cohort leading to death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below:

[Number of subjects]

- In the case of “summaries by causality”
A subject with occurrences of TEAE in both categories (i.e., “Related” and “Not related”) will be counted once in the “Related” category.
- In the case of “summaries by intensity”
A subject with multiple occurrences of TEAE will be counted once for

the TEAE with the maximum intensity.

- In the case of summaries other than the above

A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

3.1.2 Displays of Treatment-Emergent Adverse Events

Analysis set:	Safety analysis set in the open-label cohort
Analysis variables:	TEAEs in the open-label cohort Infusion reactions in the open-label cohort
Categories:	Intensity [Mild, Moderate, Severe] Time of onset (day) [1≤ - ≤42, 43≤ - ≤98, 99≤ - ≤210, 211≤ - ≤322, 323≤ - ≤434, 435≤ - ≤546, 547≤ - ≤Max] Study drug administration [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14] in the open-label cohort (times)
Analysis methodology:	The following summaries will be provided for the above analysis variables using frequency distributions. TEAEs will be coded by use of MedDRA and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only. Categories for time of onset (day) will be determined based on the number of days by defining the day of the first dose of the study drug in the open-label cohort as day 1. <ol style="list-style-type: none">(1) All TEAEs in the open-label cohort by SOC and PT(2) All TEAEs in the open-label cohort by SOC(3) All TEAEs in the open-label cohort by PT(4) Drug-related TEAEs in the open-label cohort by SOC and PT(5) Intensity of all TEAEs in the open-label cohort by SOC and PT(6) Intensity of drug-related TEAEs in the open-label cohort by SOC and PT(7) TEAEs in the open-label cohort leading to study drug discontinuation by SOC and PT(8) Serious TEAEs in the open-label cohort by SOC and PT(9) Serious drug-related TEAEs in the open-label cohort by SOC and

PT

- (10) All TEAEs in the open-label cohort by SOC and PT over time
- (11) Infusion reaction in the open-label cohort by SOC and PT
- (12) Infusion reaction in the open-label cohort by study drug administration in the open-label cohort (times) by SOC and PT
- (13) TEAEs in the open-label cohort whose onset date is the day of the study drug administration or the following day by SOC and PT
- (14) TEAEs in the open-label cohort whose onset date is the day of the study drug administration or the following day by study drug administration in the open-label cohort (times) by SOC and PT
- (15) TEAEs in the open-label cohort whose incidence summarized by PT is 3% or higher by SOC and PT

The frequency distribution and incidence will be provided according to the rules below:

[Number of subjects]

- In the case of “summaries by SOC and PT, by SOC, and by PT”
A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.
Percentages of TEAE in the open-label cohort will be based on the number of subjects in the safety analysis set in the open-label cohort.
- In the case of “summaries of intensity by SOC and PT”
A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages of TEAE in the open-label cohort will be based on the number of subjects in the safety analysis set in the open-label cohort.
- In the case of “summaries by SOC and PT over time”
A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE in the open-label cohort for each time interval, the number of subjects at risk (i.e., “subjects who either have an exposure in the study or have an occurrence of TEAE in the open-label cohort, during or after the corresponding time interval”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAE in the open-label cohort is within the time interval” will be used as the numerator.

- In the case of “summaries of the study drug administration in the open-label cohort (times) by SOC and PT”

A subject with a TEAE that occurs in more than one time of study drug administration is counted for all the administrations (times) that the TEAE occurs. For each administration, a subject with multiple occurrences of TEAEs within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE in the open-label cohort for each administration (time) in the open-label cohort, the number of subjects at risk (i.e., “subjects who received the first, etc., study drug administration in the open-label cohort”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAEs in the open-label cohort is at the time of first, etc., administration in the open-label cohort” will be used as the numerator.

3.2 Pretreatment Event

3.2.1 Display of Pretreatment Event

Not applicable.

3.3 Clinical Laboratory Evaluations and Other Safety Endpoints

3.3.1 Clinical Laboratory Evaluations

3.3.1.1 Hematology and Blood Biochemistry

Analysis set:	Safety analysis set in the open-label cohort		
Analysis variables:	Hematology		
	Red blood cells (RBC)	White blood cells (WBC)	Hemoglobin
	Hematocrit	Platelets	
	WBC differentials (neutrophils/leukocytes, eosinophils/leukocytes, basophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes)		
	Blood biochemistry		
	Albumin	AST(GOT)	ALT(GPT)
	ALP	Amylase	Glucose
	Total bilirubin	Total protein	γ-GTP
	Total cholesterol	Triglyceride	Creatinine
	BUN	Uric acid	Potassium
	Sodium	Calcium	Phosphorus
	Magnesium	Chloride	
	Inflammatory markers		

	C-reactive protein (CRP)	
Categories:	Adjudication results based on normal reference range	[Below lower limit of normal range, Within normal range, Over upper limit of normal range]
Visit:	Categories in SAP Appendix 2 (1) Weeks 0, 0x, 2x, 6x, 14x, 22x, 30x, 38x, 46x, 54x, 62x, 70x, 78x, 86x, 94x, and 16 weeks after the last dose of the study drug (hematology, blood biochemistry) Weeks 0, 0x, 2x, 6x, 14x, 22x, 30x, 38x, 46x, 54x, 62x, 70x, 78x, 86x, and 94x (inflammatory markers)	
Analysis methodology:	The following analysis will be performed for the above analysis variables. Refer to Appendix 2 of this SAP for laboratory test items subject to this analysis, categories in the shift table, MAV criteria, and definition of elevated liver enzyme.	
	<ol style="list-style-type: none"> (1) Summary statistics for each visit and summary statistics of differences before and after administration for each visit (2) Case plots (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each post-baseline visit (4) Shift tables showing categories of SAP Appendix 2 (1) at Week 0 and each post-baseline visit (5) Overall frequency distributions of MAV in the open-label cohort (6) Overall frequency distributions of elevated liver enzymes in the open-label cohort 	

3.3.1.2 Urinalysis

Analysis set:	Safety analysis set in the open-label cohort	
Analysis variables:	pH Urine specific gravity Glucose Protein Occult blood Bilirubin Ketone body	
Categories:	Adjudication results based on normal reference range	[Below lower limit of normal range, Within normal range, Over upper limit of normal range]
Visit:	Weeks 0, 0x, 94x, and 16 weeks after the last dose of the study drug	

Analysis methodology: The following analysis of (1), (2), and (3) will be performed for pH and specific gravity. The following analysis of (3) will be performed for the above analysis variables other than pH and specific gravity.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration
- (2) Case plots
- (3) Shift tables showing adjudication results based on normal reference range at Week 0 and each post-baseline visit

3.3.2 Vital Signs, Physical Examination, and Other Observation Items Related to Safety

3.3.2.1 Vital Signs, Body Weight

Analysis set: Safety analysis set in the open-label cohort

Analysis variables: Systolic blood pressure
Diastolic blood pressure
Pulse
Body temperature
Weight

Visit: Weeks 0, 0x, 2x, 6x, 10x, 14x, 18x, 22x, 26x, 30x, 34x, 38x, 42x, 46x, 50x, 54x, 58x, 62x, 66x, 70x, 74x, 78x, 82x, 86x, 90x, 94x, and 16 weeks after the last dose of the study drug

Analysis methodology: The following analysis will be performed for the above analysis variables.

- (1) Summary statistics for each visit and summary statistics of differences before and after administration for each visit
- (2) Case plots

3.3.2.2 12-Lead ECG

Analysis set: Safety analysis set in the open-label cohort

Analysis variables: Findings of 12-lead ECG [Within normal limits, Abnormal but not clinically significant, Abnormal and clinically significant]

Visit: Weeks 0, 0x, 94x, and 16 weeks after the last dose of the study drug

Analysis methodology: The following analysis will be performed for the findings of 12-lead ECG

- (1) Shift tables at Week 0 and each post-baseline visit

4 DISPLAY OF TREATMENT-EMERGENT ADVERSE EVENT (IN JAPANESE)

4.1 Display of Treatment-Emergent Adverse Event (in Japanese)

Analysis set: Safety analysis set in the open-label cohort
Analysis TEAE in the open-label cohort by SOC and PT
variables: Infusion reaction in the open-label cohort by SOC and PT
Analysis The similar summaries as 3.1.2 section will be provided for the above
methodology: analysis variables. SOC and PT will be displayed in Japanese.

5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS

5.1 AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody in the “full analysis set in the open-label cohort”	
Analysis variables:	AVA	[Negative, Positive]
	AVA titer	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody	[Negative, Positive]
Visit:	Weeks 0, 0x, 10x, 30x, 62x, 94x, and 16 weeks after the last dose of the study drug (AVA, AVA titer, neutralizing antibody)	
Analysis methodology:	The following analysis will be performed for the above analysis variables. The category of AVA titer will be set according to the observed AVA titer. (1) Frequency distributions	

5.2 Efficacy by AVA and Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody in the “full analysis set in the open-label cohort”	
Analysis variables:	Clinical response based on partial Mayo score at Week 94x (LOCF)	[Clinical response, Non-response]
Stratum:	AVA in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum. (1) Frequency distributions	

5.3 AVA and Neutralizing Antibody by Concomitant Use of Immunomodulators

Analysis set:	Subjects who underwent proper determination of AVA and neutralizing antibody in the “full analysis set in the open-label cohort”	
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Analysis variables:	AVA in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
	Persistently positive	[Yes, No]
	Transient positive	[Yes, No]
	Neutralizing antibody in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
Stratum:	Concomitant use of immunomodulators at Week 0	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at Week 0 (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids at Week 0	[Yes, No]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum.	
	(1) Frequency distributions	

6 SAFETY ANALYSIS OF MLN0002 TREATMENT

6.1 Measurement of Compliance Status for Treatment

6.1.1 MLN0002 Exposure and Compliance in the Treatment Period

Analysis set:	Subjects who received at least one dose of MLN0002	
Analysis variables:	Duration of MLN0002 exposure (days)	[1 ≤ - ≤84, 85 ≤ - ≤168, 169 ≤ - ≤252, 253 ≤ - ≤336, 337 ≤ - ≤420, 421 ≤ - ≤504, 505 ≤ - ≤588, 589 ≤ - ≤672, 673 ≤ - ≤756, 757 ≤ - ≤840, 841 ≤ - ≤924, 925 ≤ - ≤1008, 1009 ≤ - ≤Max]
	Duration on study after the first dose of MLN0002 (days)	[1 ≤ - ≤84, 85 ≤ - ≤168, 169 ≤ - ≤252, 253 ≤ - ≤336, 337 ≤ - ≤420, 421 ≤ - ≤504, 505 ≤ - ≤588, 589 ≤ - ≤672, 673 ≤ - ≤756, 757 ≤ - ≤840, 841 ≤ - ≤924, 925 ≤ - ≤1008, 1009 ≤ - ≤Max]
	Number of MLN0002 infusion (times)	[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]
	Number of completed MLN0002 infusions (times)	[0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]
	Number of completed or incompleted MLN0002 infusions in total infusions	[Completed, Incompleted]
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Frequency distributions for categorical variables and summary statistics for continuous variables In the frequency distributions for number of completed or incompleted MLN0002 infusions in total infusions, the sum of the number of completed MLN0002 infusions will be counted as frequency for “Completed,” and the sum of the number of incompleted MLN0002 infusions will be counted as frequency for “Incompleted.” When calculating percentage, the sum of the number of completed infusions and the number of incompleted infusions (i.e., number of total MLN0002 infusions) will be used as the denominator.	

6.2 Treatment-Emergent Adverse Event

6.2.1 Overview of Treatment-Emergent Adverse Events

Analysis set:	Subjects who received at least one dose of MLN0002
Analysis variables:	TEAEs after the first dose of MLN0002

Categories:	Causality	[Related, Not related]
	Intensity	[Mild, Moderate, Severe]
Analysis methodology:	The following summaries will be provided for the above analysis variables.	
	(1)	Overview of TEAEs after the first dose of MLN0002
	1)	All TEAEs after the first dose of MLN0002 (number of events, number and percentage of subjects)
	2)	Causal relationship between all TEAEs after the first dose of MLN0002 and study drug (number of events, number and percentage of subjects)
	3)	Intensity of all TEAEs after the first dose of MLN0002 (number of events, number and percentage of subjects)
	4)	TEAEs after the first dose of MLN0002 leading to study drug discontinuation (number of events, number and percentage of subjects)
	5)	Serious TEAEs after the first dose of MLN0002 (number of events, number and percentage of subjects)
	6)	Causal relationship between serious TEAEs after the first dose of MLN0002 and study drug (number of events, number and percentage of subjects)
	7)	Serious TEAEs after the first dose of MLN0002 leading to study drug discontinuation (number of events, number and percentage of subjects)
	8)	TEAEs after the first dose of MLN0002 leading to death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below:

[Number of subjects]

- In the case of “summaries by causality”

A subject with occurrences of TEAE in both categories (i.e., “Related” and “Not related”) will be counted once in the “Related” category.

- In the case of “summaries by intensity”

A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- In the case of summaries other than the above

A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

6.2.2 Displays of Treatment-Emergent Adverse Events

Analysis set:	Subjects who received at least one dose of MLN0002
Analysis variables:	TEAEs after the first dose of MLN0002
Categories:	Intensity [Mild, Moderate, Severe]
	Time of onset (day) [1≤ - ≤84, 85≤ - ≤168, 169≤ - ≤252, 253≤ - ≤336, 337≤ - ≤420, 421≤ - ≤504, 505≤ - ≤588, 589≤ - ≤672, 673≤ - ≤756, 757≤ - ≤840, 841≤ - ≤924, 925≤ - ≤1008, 1009≤ - ≤Max]
	MLN0002 administration (times) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23]

Analysis methodology: The following summaries will be provided for the above analysis variables using frequency distributions.

TEAEs will be coded by use of MedDRA and will be summarized based on SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

Categories for time of onset (day) will be determined based on the number of days by defining the day of the first dose of MLN0002 as day 1.

- (1) All TEAEs after the first dose of MLN0002 by SOC and PT
- (2) All TEAEs after the first dose of MLN0002 by SOC
- (3) All TEAEs after the first dose of MLN0002 by PT
- (4) Drug-related TEAEs after the first dose of MLN0002 by SOC and PT
- (5) Intensity of all TEAEs after the first dose of MLN0002 by SOC and PT
- (6) Intensity of drug-related TEAEs after the first dose of MLN0002 by SOC and PT
- (7) TEAEs after the first dose of MLN0002 leading to study drug discontinuation by SOC and PT
- (8) Serious TEAEs after the first dose of MLN0002 by SOC and PT
- (9) Serious drug-related TEAEs after the first dose of MLN0002 by SOC and PT
- (10) All TEAEs after the first dose of MLN0002 by SOC and PT over time

- (11) Infusion reaction after the first dose of MLN0002 by SOC and PT
- (12) Infusion reaction after the first dose of MLN0002 by MLN0002 administration (times) by SOC and PT
- (13) TEAEs after the first dose of MLN0002 whose onset date is the day of MLN0002 administration or the following day by SOC and PT
- (14) TEAEs after the first dose of MLN0002 whose onset date is the day of MLN0002 administration or the following day by MLN0002 administration (times) by SOC and PT
- (15) TEAEs after the first dose of MLN0002 whose incidence summarized by PT is 3% or higher by SOC and PT

The frequency distribution and incidence will be provided according to the rules below:

[Number of subjects]

- In the case of “summaries by SOC and PT, by SOC, and by PT”
 - A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.
 - Percentages of TEAE after the first dose of MLN0002 will be based on the number of subjects who received at least one dose of MLN0002.
- In the case of “summaries of intensity by SOC and PT”
 - A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.
 - Percentages of TEAE after the first dose of MLN0002 will be based on the number of subjects who received at least one dose of MLN0002.
- In the case of “summaries by SOC and PT over time”
 - A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE after the first dose of MLN0002 for each time interval, the number of subjects at risk (i.e., “subjects who either have an exposure in the study or have an occurrence of TEAE after the first dose of MLN0002, during or after the corresponding time interval”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAEs after the first dose of

MLN0002 is within the time interval” will be used as the numerator.

- In the case of “summaries of MLN0002 administration (times) by SOC and PT”

A subject with a TEAE that occurs in more than one time of MLN0002 administration is counted for all the administrations (times) that the TEAE occurs. For each administration, a subject with multiple occurrences of TEAEs within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAE after the first dose of MLN0002 for each administration (time), the number of subjects at risk (i.e., “subjects who received the first, etc., MLN0002 administration”) will be used as the denominator. The number of subjects whose “onset of any one of the TEAE after the first dose of MLN0002 is at the time of first, etc., MLN0002 administration” will be used as the numerator.

6.3 Display of Treatment-Emergent Adverse Event (in Japanese)

Analysis set: Subjects who received at least one dose of MLN0002
Analysis variables: TEAE after the first dose of MLN0002 by SOC and PT
Infusion reaction after the first dose of MLN0002 by SOC and PT
Analysis methodology: The similar summaries as 6.2.2 section will be provided for the above analysis variables. SOC and PT will be displayed in Japanese.

7 ANALYSIS OF FOLLOW-UP SURVEY AND PML CHECKLIST

7.1 Analysis of Follow-up Survey

Analysis set: Subjects who received at least one dose of MLN0002
Analysis variables: 1. Have you been diagnosed with colon dysplasia (one of the precancerous lesions) or colon cancer, lymphoma, or other types of cancer since the last contact or visit in the study? [Yes, No]
Colon dysplasia [Yes, No]
Colon cancer [Yes, No]
Lymphoma [Yes, No]
Other types of cancer [Yes, No]
2. Have you been diagnosed as having progressive multifocal leukoencephalopathy (also known as PML) since the last contact or visit in the study? [Yes, No]

	3. Have you undergone enterectomy since the last contact or visit in the study?	[Yes, No]
	Colectomy	[Yes, No]
	Small bowel resection	[Yes, No]
	4. Have you been diagnosed as having an infection requiring hospitalization since the last study visit?	[Yes, No]
	5. For female subjects: Have you become pregnant since the last study visit?	[Yes, No, Not applicable]
	6. For male subjects: Has your female partner become pregnant since the last study visit?	[Yes, No, Not applicable]
Visit:	6, 12, 18, and 24 months after the last dose of study drug (1. to 3.) 6 months after the last dose of the study drug (4. to 6.)	
Analysis methodology:	The following analysis will be performed for the above analysis variables. (1) Frequency distributions at each visit The analysis for variable 5 will be performed in female subjects. The analysis for variable 6 will be performed in male subjects.	

7.2 Analysis of PML checklist

Analysis set:	Subjects who received at least one dose of MLN0002 and have available data on the subjective PML checklist	
Analysis variables:	Subjective symptoms	[Yes, No]
	Objective findings	[Yes, No, Unknown]
Analysis methodology:	The following analysis will be performed for the above analysis variables. If a subject has multiple findings reported at different visits, he/she will be classified as follows:	
	-	“Yes”: “Yes” at any visit
	-	“No”: “No” at all visits after excluding missing values and other than the above
	-	“Unknown”: Missing at all visits and other than the above (no evaluation)
	(1)	Frequency distributions

8 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT

- Confidence coefficient: 95% (two-sided estimate)

History of Revision (version management)

Version	Date	Prepared/modified by	Comments
First Version	24 February 2017	PPD	Preparation of first version

[Appendix 1] Comparison Table for Changes

N/A

[Appendix 2] Definitions of Categories in Shift Table, MAV Criteria, and Criteria for Elevated Liver Enzyme

(1) Categories in Shift Table

The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

Test item	Categories
Albumin	\geq LLN, <LLN to 3 g/dL, <3 g/dL to 2 g/dL, <2 g/dL to 1 g/dL, <1 g/dL
ALT(GPT)	\leq ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
AST(GOT)	\leq ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
Total bilirubin	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 3.0×ULN, >3.0×ULN to 10.0×ULN, >10.0×ULN
Creatinine	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 3.0×ULN, >3.0×ULN to 6.0×ULN, >6.0×ULN
ALP	\leq ULN, >ULN to 2.5×ULN, >2.5×ULN to 5.0×ULN, >5.0×ULN to 20.0×ULN, >20.0×ULN
WBC	\geq LLN, <LLN to 3000/ μ L, <3000/ μ L to 2000/ μ L, <2000/ μ L to 1000/ μ L, <1000/ μ L
WBC	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Platelets	\geq LLN, <LLN to 7.5×10 ⁴ / μ L, <7.5×10 ⁴ / μ L to 5.0×10 ⁴ / μ L, <5.0×10 ⁴ / μ L to 2.5×10 ⁴ / μ L, <2.5×10 ⁴ / μ L
Platelets	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN to 3.0×ULN, >3.0×ULN
Lymphocytes	\geq 800/ μ L, <800/ μ L to 500/ μ L, <500/ μ L to 200/ μ L, <200/ μ L
Lymphocytes (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Eosinophils (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Monocytes (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Basophils (%)	\leq ULN, >ULN to 1.25×ULN, >1.25×ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN
Hemoglobin	\geq LLN, <LLN to 10 g/dL, <10 g/dL to 8 g/dL, <8 g/dL to 6.5 g/dL, <6.5 g/dL
Neutrophils	\geq 1500/ μ L, <1500/ μ L to 1000/ μ L, <1000/ μ L to 500/ μ L, <500/ μ L
Neutrophils (%)	\leq ULN, >ULN to 1.5×ULN, >1.5×ULN to 2.0×ULN, >2.0×ULN to 3.0×ULN, >3.0×ULN

Missing data will not be included in any category.

(2) MAV Criteria

1) Hematology, Blood Biochemistry

For each test item, MAV will be determined according to the table below for evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) obtained from the day after the first dose of the study drug in the open-label cohort until 167 days* after the last dose of the study drug (including Follow-up Day 167). The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

* Day after the last dose of the study drug will be defined as Follow-up Day 1.

Test item	MAV Criteria	
	Lower criteria	Upper criteria
Hemoglobin (g/dL)	≤7	-
Lymphocytes (/μL)	<500	-
WBC (/μL)	<2000	-
Platelets (×10 ⁴ /μL)	<7.5	-
Neutrophils (/μL)	<1000	-
ALT(GPT) (U/L)	-	>3.0×ULN
AST(GOT) (U/L)	-	>3.0×ULN
Total bilirubin (mg/dL)	-	>2.0×ULN
Amylase (U/L)	-	>2.0×ULN

Classifying Subjects for the Overall Open-label Cohort

For each test item and subject, MAV will be determined according to the conditions [1] to [3] provided below.

- [1] A subject will be classified as those “with MAV” if he/she has at least one data that “meets the MAV Criteria” among the evaluable data obtained from the day after the first dose of the study drug in the open-label cohort until 167 days after the last dose of the study drug (including Follow-up Day 167).
- [2] A subject will be classified as those “without MAV” if he/she does not meet condition [1] and has at least one data that does “not meet the MAV Criteria” among the evaluable data obtained from the day after the first dose of the study drug in the open-label cohort until 167 days after the last dose of the study drug (including Follow-up Day 167).
- [3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of MAV for that item.

(3) Criteria for Elevated Liver Enzyme

For each test item, elevated liver enzyme will be determined according to the table below for evaluable data (i.e., non-missing data and data determined to be eligible based on “Handling Rules for Analysis Data”) obtained from the day after the first dose of the study drug in the open-label cohort until 167 days* after the last dose of the study drug (including Follow-up Day 167). If there is more than one item that need to be considered for a criteria, test items measured on the same day will be used. The following abbreviations are used in the table below: LLN for lower limit of the normal range, ULN for upper limit of the normal range, ALT for alanine aminotransferase, AST for aspartate aminotransferase, Tbili for total bilirubin, and ALP for alkaline phosphatase.

* Day after the last dose of the study drug will be defined as Follow-up Day 1.

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
ALT > 3×ULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5×ULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8×ULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3×ULN with Tbili > 2×ULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3×ULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5×ULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8×ULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN
AST > 3×ULN with Tbili > 2×ULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3×ULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5×ULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN
ALT or AST > 8×ULN	Either ALT or AST is greater than 8 times the ULN	Both ALT and AST are non-missing and less than or equal to 8 times the ULN
ALT or AST > 3×ULN with Tbili > 2×ULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: <ul style="list-style-type: none"> - Both ALT and AST are non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALT and AST > 3×ULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
ALT and AST > 5×ULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8×ULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3×ULN with Tbili > 2×ULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: <ul style="list-style-type: none"> - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3×ULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3×ULN with ALT > 3×ULN	Both ALP and ALT are greater than 3 time the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3×ULN with AST > 3×ULN	Both ALP and AST are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

Classifying Subjects for the Overall Open-label Cohort

For each criteria and subject, “elevated liver enzyme” will be determined according to the conditions [1] to [3] provided below.

- [1] A subject will be classified as those “with elevated liver enzyme” if he/she has at least one data that “meets the criteria for elevated liver enzyme” among the evaluable data obtained from the day after the first dose of the study drug in the open-label cohort until 167 days after the last dose of the study drug (including Follow-up Day 167).
- [2] A subject will be classified as those “without elevated liver enzyme” if he/she does not meet condition [1] and has at least one data that does “not meet the criteria for elevated liver enzyme” among the evaluable data obtained from the day after the first dose of the study drug in the open-label cohort until 167 days after the last dose of the study drug (including Follow-up Day 167).
- [3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of elevated liver enzyme for that item.