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 Crohn's disease

NCT Number: NCT02038920

Statistical analysis plan Approve Date: 25-JAN-2018

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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

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 Crohn's disease
Protocol No.	: MLN0002/CCT-001
Sponsor	: Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

Trial Statistician

Person responsible for pharmacokinetic/pharmacodynamic analyses

First version: 25 January 2018

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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.
- 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.
- Per protocol set in the induction phase: All subjects in the 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.

- 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.
- Baseline: A visit at "Week 0" in "HANDLING OF TIME WINDOW"

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.

CDAI score*[1], each CDAI subscore*[2], hematocrit level*[3] (tested by the central laboratory), inflammatory marker (CRP)

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*[4]	Study Day: 43	29 to 56	
Week 10*[5]	Study Day: 71	57 to 84	

*[1] CDAI-70 response, CDAI-100 response, and clinical remission will be determined based on CDAI scores.

*[2] Each CDAI subscore used for the calculation of CDAI scores based on the hematocrit (Ht) level at each study site will be used.

*[3] The Ht level will be handled as follows:

- If the Ht level tested on the same date as the evaluation day of the CDAI score based on the Ht level at each study site is available, that Ht level will be used.
- If the Ht level tested on the same date as the evaluation day of the CDAI score based on the Ht level at each study site is not available, it will be handled according to the general rules described directly beneath "HANDLING OF TIME WINDOW."

*[4] If the Ht level at Week 6 is missing, the same Ht level as that obtained at Week 2 will be used for Week 6.

*[5] If the Ht level at Week 10 is missing, the same Ht level as that obtained at Week 6 will be used for Week 10. However, if the Ht level at Week 2 is used for Week 6 according to the handling described in *4, the Ht level at Week 10 will be handled as missing.

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	

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)

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.

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 (days): 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 (days): 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/m^2) = Weight (kg) / (Height [cm]/100)^2 (round off to the first decimal place)

- Duration of CD (years): (Date of informed consent [year and month] − Date of CD diagnosis [year and month]) / 12 (round off to the first decimal place)
  - Only the year and month for the date of informed consent will be used.
  - The unit for "Date of informed consent (year and month) − Date of CD diagnosis (year and month)" will be "months."
  - If the year of CD diagnosis is unknown, the duration of CD will be handled as "Missing." If only the month of CD diagnosis is unknown, the duration of CD will be calculated by setting the month of CD 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 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 is not "Yes," subjects for whom immunomodulatory intolerance is "Yes" are classified as "Intolerance."
- Prior TNFα antagonist failure: If inadequate response, loss of response, or intolerance to the TNFα antagonist is "Yes," prior TNFα antagonist failure will be defined as "Yes." Any response other than the above will be defined as "No."

- Number of drugs of TNFα antagonist failure: Among the drugs entered to prior treatment failure (TNFα antagonist) for CD, 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 (TNFα antagonist) for CD are classified as "No."
- Classification of prior TNFα antagonist failure: Subjects for whom TNFα antagonist failure is "Yes" are classified as follows:
  - Subjects for whom TNFα antagonist inadequate response is "Yes" are classified as "Inadequate response."
  - Among subjects for whom TNFα antagonist inadequate response is not "Yes," subjects for whom TNFα antagonist loss of response is "Yes" are classified as "Loss of response."
  - Among subjects for whom TNFα antagonist inadequate response is not "Yes" as well as TNFα antagonist loss of response not being "Yes," subjects for whom TNFα antagonist intolerance is "Yes" are classified as "Intolerance."
- Prior immunomodulators failure (excluding prior TNFα antagonist failure): If prior TNFα antagonist failure is "No" and prior immunomodulators failure is "Yes," prior immunomodulators failure (excluding prior TNFα antagonist failure) will be defined as "Yes." All others will be defined as "No."
- Prior corticosteroid failure only: If prior TNFα 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 TNFα antagonist failure: If prior immunomodulators failure is "Yes" and prior TNFα antagonist failure is "Yes," prior immunomodulators and TNFα 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 ≥75%), the study drug infusion will be defined as "Completed." All others will be defined as "Incompleted."

The Ht level and CDAI score will be handled as follows:

- The CDAI score, CDAI subscore, and Ht levels used for analysis will be determined at the central laboratory unless otherwise noted.
- CDAI score: The sum of CDAI subscores of (1) to (8) defined in the table below.

(1)	Number of liquid or very soft stools during the last 1 week	× 2
(2)	Abdominal pain during the last 1 week (7-day total of daily abdominal pain scores on a following scale) 0=None, 1=Mild, 2=Moderate, 3=Severe	× 5
(3)	Subjective general well being during the last 1 week (7-day total of daily general well-being scores on a following scale) 0=Generally well, 1=Slightly under par, 2=Poor, 3=Very poor, 4=Terrible	× 7
(4)	Current number of the following extraintestinal manifestations of CD 1) Arthritis/arthralgia 2) Iritis/uveitis 3) Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis 4) Anal fissure, anal fistula, or perianal abscess 5) Other fistula 6) Fever over 37.8°C during the last 1 week	× 20
(5)	Use of antidiarrheal drugs (e.g., lopemin) or opiates for diarrhea 0=No, 1=Yes	× 30
(6)	Abdominal mass 0=None, 2=Questionable, 5=Definite	× 10
(7)	Hematocrit (%)[Note 1)] Males: subtract value from 47, Females: subtract value from 42	× 6
(8)	Body weight : Standard weight (body-weight ratio)[Note 2)] [1 - (Body weight / Standard weight)] × 100	× 1

Note 1) If hematocrit subtotal <0, enter 0.
Note 2) If body weight subtotal <-10, enter -10.

- The CDAI score will be calculated using subscores on the same day of evaluation. For subscore (7), however, the CDAI score will be calculated using the Ht level obtained within the same visit window if the Ht level on the same day of evaluation is not available.
- If any CDAI subscore is missing, the CDAI score will be handled as missing.
- CDAI-70 response: Subjects will be classified as "CDAI-70 response" if "a ≥70-point decrease in CDAI score from baseline" is achieved. All others will be classified as "Non-CDAI-70 response." However, if any CDAI score change 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-CDAI-70 response."
- CDAI-100 response: Subjects will be classified as "CDAI-100 response" if "a ≥100-point decrease in CDAI score from baseline" is achieved. All others will be classified as "Non-CDAI-100 response." However, if any CDAI score change 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-CDAI-100 response."
- Clinical remission: Subjects will be classified as "Clinical remission" if "CDAI score of ≤150" is achieved. All others will be classified as "Non-remission." However, if any of the CDAI scores 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."

After the CDAI-100 response and clinical remission at each visit are determined using the above methods, the following durable remission and durable CDAI-100 response will be determined.

- Durable remission in the induction phase: Subjects will be classified as "Durable remission" if "Clinical remission at Week 6 and Week 10" is achieved. All others will be classified as "Non-durable remission." Then, if the adjudication result at Week 6 or Week 10 is missing, subjects will be classified as "Non-durable remission."
- Durable CDAI-100 response in the induction phase: Subjects will be classified as "Durable CDAI-100 response" if "CDAI-100 response at Week 6 and Week 10" is achieved. All others will be classified as "Non-durable CDAI-100 response." Then, if the adjudication result at Week 6 or Week 10 is missing, subjects will be classified as "Non-durable CDAI-100 response."
- Durable CDAI-70 response in the induction phase: Subjects will be classified as "Durable CDAI-70 response" if "CDAI-70 response at Week 6 and Week 10" is achieved. All others will be classified as "Non-durable CDAI-70 response." Then, if the adjudication result at Week 6 or Week 10 is missing, subjects will be classified as "Non-durable CDAI-70 response."

In addition, the following determination will be made.

- CDAI-100 response at Week 10 with CRP level of ≤1.6 mg/dL at Week 10: Subjects will be classified as "Yes" if "CDAI-100 response at Week 10 and CRP level of ≤1.6 mg/dL at Week 10 are both achieved." All others will be defined as "No." Then, if the adjudication result of CDAI-100 response at Week 10 or CRP level at Week 10 is missing, subjects will also be classified as "No."
- Clinical remission at Week 10 with CRP level of ≤1.6 mg/dL at Week 10: Subjects will be classified as "Yes" if clinical remission at Week 10 and CRP level of ≤1.6 mg/dL at Week 10 are both achieved. All others will be defined as "No." Then, if the adjudication result of clinical remission at Week 10 or CRP level at Week 10 is missing, subjects will also be classified as "No."

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	• 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 the calculation of that subscore. • If 2 questions are missing among those used for the calculation of each subscore, that subscore will be handled as missing.
IBDQ total score	• Among the questions used for the calculation of IBDQ total score, the missing data will be imputed using the mean of the non-missing questions used for the calculation of each subscore. However, if 5 or more questions are missing or more than 2 subscores are missing among the questions used for the 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 in IBDQ total score: “Yes” if the change from baseline in IBDQ total score is ≥16, “No” if it is <16, and “Missing” if it is missing.
- -16 or lower in change from baseline in IBDQ total score: “Yes” if the change from baseline in IBDQ total score is ≤-16, “No” if it is >-16, and “Missing” if it is missing.

Prior TNFα antagonist use, concomitant use of immunomodulators at baseline, and concomitant use of oral corticosteroids at baseline will be defined as follows:

- Prior TNFα 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 baseline: Subjects who received any concomitant medication (for treatment of CD) which is classified as "immunomodulator" in the concomitant medication (for treatment of CD) 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 CD) 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 baseline: Subjects who received any concomitant medication (for treatment of CD) which is classified as "corticosteroid" and whose route of administration is "oral" in the concomitant medication (for treatment of CD) 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 CD) which was started after the first dose of the study drug in the induction phase is not subject to this handling.

Concurrent extraintestinal manifestations (based on CDAI subscore [4]), concurrent extraintestinal manifestations (based on case report form [CRF] concurrent medical condition section), surgical history for CD, medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent, and concurrent medical condition related to fistula will be defined as follows:

- Concurrent extraintestinal manifestations (based on CDAI subscore [4]): Subjects whose CDAI subscore [4] at baseline is greater than 0 will be classified as "Yes." All others will be classified as "No."
- Concurrent extraintestinal manifestations (based on CRF concurrent medical condition section): Subjects recorded to have concurrent extraintestinal manifestations of CD in the CRF concurrent medical condition section will be classified as "Yes." All others will be classified as "No."
- Surgical history for CD: Subjects coded with at least one PT in the following table for medical history will be classified as "Yes." All others will be classified as "No."

Preferred Term
Anal skin tag excision
Colectomy
Crohn's disease
Enterocutaneous fistula
Ileal operation
Ileectomy
Ileocolectomy
Ileocolostomy
Ileostomy
Ileostomy closure
Intestinal resection
Proctectomy
Sigmoidectomy
Small intestinal resection
Small intestine operation
Stricturoplasty
Urinary cystectomy

- Medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent: Subjects coded with at least one PT in the following table for medical history or concurrent medical condition will be classified as “Yes.” All others will be classified as “No.”

Medical history

Preferred Term
Anal fistula
Fistula of small intestine

Concurrent medical condition

Preferred Term
Anal fistula
Enterocutaneous fistula
Female genital tract fistula

- Concurrent medical condition related to fistula: Subjects coded with at least one PT in the following table for concurrent medical condition will be classified as “Yes.” All others will be

classified as “No.”

Preferred Term
Anal fistula
Enterocutaneous fistula
Female genital tract fistula

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.

After determining the negative or positive status of the neutralizing antibody at each visit with the above-mentioned logic, the following determination will be made:

- AVA in the induction phase
  - 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 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 will be classified as “AVA-negative.”
  - Subjects whose AVA values are missing at all visits in the induction phase will be classified as missing.
- Neutralizing antibody in the induction phase
  - Subjects who were determined to be neutralizing antibody-positive at any visit after the day of the first dose of the study drug in the induction phase will be classified as “neutralizing antibody-positive.”
  - Subjects who were determined to be neutralizing antibody-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 will be classified as “neutralizing antibody-negative.”
  - Subjects whose neutralizing antibody values are missing at all visits in the induction phase will be classified as missing.

Lymphocytes and neutrophils will be calculated with the following formula:

- Lymphocytes = WBC × lymphocytes (%)
- Neutrophils = WBC × 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	
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 treatment group in the induction phase and in the consolidated 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 treatment group in the induction phase and in the consolidated 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 complete 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 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]
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 treatment group in the induction phase and in the consolidated 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 treatment group in the induction phase and in the consolidated 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 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	
	Full analysis set in the induction phase	[Included]
	Per protocol set in the induction phase	[Included]
	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 treatment group in the induction phase and the following analysis of (3) will be performed by each treatment group in the induction phase and in the consolidated 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 baseline	[Min≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
	BMI (kg/m^2) at baseline	[Min≤ - ≤18.4, 18.5≤ - ≤24.9, 25.0≤ - ≤Max]

Smoking classification	[Never smoked, Current smoker, Ex-smoker]
Duration of CD (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 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]
Prior TNFα antagonist use	[Yes, No]
Infliximab	[Yes, No]
Adalimumab	[Yes, No]
Golimumab	[Yes, No]
Concomitant use of enteral nutrient at baseline	[Yes, No]
Concomitant use of 5-ASA at baseline	[Yes, No]
Concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids at baseline	[Yes, No]
No concomitant use of oral	[Yes, No]

corticosteroids and No concomitant use of immunomodulators at baseline	
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline	[Yes, No]
CDAI score at baseline	[Min≤ - ≤220, 220< - ≤330, 330< - ≤450, 450< - ≤Max]
CDAI subscore (1): Number of liquid or very soft stools during the last 1 week at baseline	
CDAI subscore (2): Abdominal pain during the last 1 week at baseline	
CDAI subscore (3): Subjective general well being during the last 1 week at baseline	
CDAI subscore (4): Current number of extraintestinal manifestations of CD (e.g., arthritis/arthralgia) at baseline	[0, 1, 2, 3, 4, 5, 6]
CDAI subscore (5): Use of antidiarrheal drugs (e.g.,	[No, Yes]

	lopemin) or opiates for diarrhea at baseline	
	CDAI subscore (6): Abdominal mass at baseline	[None, Questionable, Definite]
	CDAI subscore (7): Hematocrit level at baseline	
	CDAI subscore (8): Body weight : Standard weight (body-weight ratio) at baseline	
	Disease localization	[Small intestinal, Large intestinal, Small/Large intestinal]
	Concurrent extraintestinal manifestations (based on CDAI subscore [4])	[Yes, No]
	Concurrent extraintestinal manifestations (based on CRF concurrent medical condition section)	[Yes, No]
	CRP (mg/dL) at baseline	[Min≤ - ≤0.3, 0.3< - ≤0.5, 0.5< - ≤1.0, 1.0< - ≤1.6, 1.6< - ≤Max]
	Surgical history for CD	[Yes, No]
	Medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent	[Yes, No]
	Concurrent medical condition related to fistula	[Yes, No]

Analysis methodology: The following analysis will be performed for the above analysis variables by each treatment group in the induction phase and in the consolidated treatment groups in the induction phase. The same analysis will be performed with stratification according to “prior TNFα antagonist use.”

(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 CD)

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

Analysis methodology: The following analysis will be performed for the above analysis variables by each treatment group in the induction phase and in the consolidated 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 CD) (by SOC and PT)

(3) Frequency distributions for concurrent medical conditions (other than concurrent extraintestinal manifestations of CD) (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 CD) in the induction phase

Classification of concomitant medications (for treatment of CD) in the induction phase [5-ASA, Corticosteroids,

		Immunomodulators, Enteral nutrients, Other]
	Concomitant medications (for treatment of CD) in the induction phase that fall under the category of rescue treatments	
	Classification of concomitant medications (for treatment of CD) in the induction phase that fall under the category of rescue treatments	[5-ASA, Corticosteroids, Immunomodulators, Enteral nutrients, Other]
	Concomitant medications (for other than treatment of CD) 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 treatment group in the induction phase and in the consolidated treatment groups in the induction phase.

Medication history, concomitant medications (for treatment of CD) in the induction phase, concomitant medications (for treatment of CD) in the induction phase that fall under the category of rescue treatments, and concomitant medications (for other than treatment of CD) 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 CD) in the induction phase that were ongoing at baseline and continued in the induction phase, and concomitant medications (for treatment of CD) in the induction phase that started after baseline by category

(3) Frequency distributions for concomitant medications (for treatment of CD) 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 CD) 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 CD) in the induction phase that were ongoing at baseline and continued in the induction phase, and concomitant medications (for other than treatment of CD) 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 treatment group in the induction phase and in the consolidated 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 incompleted 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. From 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:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
Stratum:	Prior TNFα 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 "CDAI-100 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 same calculation will be performed with stratification according to "prior TNFα antagonist use" and the Cochran-Mantel-Haenszel (CMH) test with two-sided significance level of 10% by using "prior TNFα antagonist use" as a stratification factor will be performed. In addition, the adjusted odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI will be calculated.

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 CDAI-100 response at Week 10 will be demonstrated when a statistically significant difference in CDAI-100 response at Week 10 is observed in the primary analysis of the induction phase.

2.1.2 Secondary Analysis

Analysis set:	Per protocol set in the induction phase Full analysis set in the induction phase	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
Stratum:	Prior TNFα antagonist use	[Yes, No]

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

(1) The CDAI-100 response at Week 10 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.

The following analysis will be performed for reference.

(2) For the CDAI-100 response at Week 10, the CMH adjusted risk difference (MLN0002 group − placebo group) with "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated in the "full analysis set in the induction phase."

(3) The CDAI-100 response at Week 10 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 CDAI 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]
	Change in CRP level over time in the subpopulation of subjects with the baseline CRP level of >0.30 mg/dL	
Stratum:	Prior TNFα antagonist use	[Yes, No]
Visit:	Weeks 0, 2, 6, and 10 (change in CRP level over time in the subpopulation of subjects with the baseline CRP level of >0.30 mg/dL)	
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 both CDAI-100 response at Week 10 in the primary analysis of 2.1.1 and clinical remission at Week 10 in the analysis methodology (3).

(1) Frequency distributions will be provided for clinical remission 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.

(2) Frequency distributions will be provided for clinical remission at Week 10 with stratification according to "prior TNFα 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.

(3) The CMH test with two-sided significance level of 10% by using "prior TNFα antagonist use" as a stratification factor will be performed for clinical remission at Week 10 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

(4) Summary statistics and 95% two-sided CI of the mean will be calculated for CRP level at each visit (baseline to Week 10) in the subpopulation of subjects with the baseline CRP level of >0.30 mg/dL. In addition, summary statistics, the 95% two-sided CI of the mean, 10^{th} and 90^{th} percentiles will be calculated for changes from baseline in CRP level at each visit (Week 2 to Week 10) in the subpopulation of subjects with the

baseline CRP level of >0.30 mg/dL.

(5) The same analysis as (4) will be performed with stratification according to "prior TNFα antagonist use" in the subpopulation of subjects with the baseline CRP level of >0.30 mg/dL.

(6) The van Elteren test (CMH test with the modified ridit score) stratified by "prior TNFα antagonist use" will be performed for changes from baseline in CRP level at each visit (Week 2 to Week 10) in the subpopulation of subjects with the baseline CRP level of >0.30 mg/dL.

2.3 Other Endpoints and Analysis Methodology

2.3.1 Endpoints Related to CDAI Scores

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	Clinical remission	[Clinical remission, Non-remission]
	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	Durable remission	[Durable remission, Non-durable remission]
	Durable CDAI-100 response	[Durable CDAI-100 response, Non-durable CDAI-100 response]
	Durable CDAI-70 response	[Durable CDAI-70 response, Non-durable CDAI-70 response]
	CDAI-100 response at Week 6 and Week 10 and clinical remission at Week 6 and Week 10 in the subpopulation of subjects without prior TNFα antagonist use and in the subpopulation of subjects who failed with a TNFα antagonist	[CDAI-100 response, Non-CDAI-100 response] [Clinical remission, Non-remission]
	CDAI-100 response at Week 6 and Week 10 and clinical remission at	[CDAI-100 response, Non-CDAI-100

	Week 6 and Week 10 in the subpopulation of subjects who failed with a corticosteroid monotherapy and an immunomodulator (except those failed with a TNFα antagonist) CDAI score change over time Each CDAI subscore change over time	response] [Clinical remission, Non-remission]
Visit:	Weeks 0, 2, 6, and 10	

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

(1) Frequency distributions will be provided for clinical remission 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.

(2) Frequency distributions will be provided for clinical remission at each visit with stratification according to "prior TNFα 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.

(3) The CMH test using "prior TNFα antagonist use" as a stratification factor will be performed for clinical remission at each visit 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

(4) The same analysis as (1) will be performed for the CDAI-100 response at each visit.

(5) The same analysis as (2) will be performed for CDAI-100 response at each visit with stratification according to "prior TNFα antagonist use."

(6) The same analysis as (3) will be performed for the CDAI-100

response at each visit.

(7) The same analysis as (1) will be performed for the CDAI-70 response at each visit.

(8) The same analysis as (2) will be performed for CDAI-70 response at each visit with stratification according to "prior TNFα antagonist use."

(9) The same analysis as (3) will be performed for the CDAI-70 response at each visit.

(10) The same analysis as (1) will be performed for durable remission.

(11) The same analysis as (2) will be performed for durable remission with stratification according to "prior TNFα antagonist use."

(12) The same analysis as (3) will be performed for durable remission.

(13) The same analysis as (1) will be performed for durable CDAI-100 response.

(14) The same analysis as (2) will be performed for durable CDAI-100 response with stratification according to "prior TNFα antagonist use."

(15) The same analysis as (3) will be performed for durable CDAI-100 response.

(16) The same analysis as (1) will be performed for durable CDAI-70 response.

(17) The same analysis as (2) will be performed for durable CDAI-70 response with stratification according to "prior TNFα antagonist use."

(18) The same analysis as (3) will be performed for durable CDAI-70 response.

(19) The same analysis as (1) will be performed for the CDAI-100 response and clinical remission at each visit in the subpopulation of subjects without prior TNFα antagonist use. The Pearson's chi-square test will be also performed.

(20) The same analysis as (1) will be performed for the CDAI-100 response and clinical remission at each visit in the subpopulation of subjects who failed with a TNFα antagonist. The Pearson's chi-square test will be also performed.

(21) The same analysis as (1) will be performed for the CDAI-100 response and clinical remission at each visit in the subpopulation of subjects who failed with a corticosteroid monotherapy. The Pearson's chi-square test will be also performed.

(22) The same analysis as (1) will be performed for the CDAI-100 response and clinical remission at each visit in the subpopulation of subjects who failed with an immunomodulator (except those failed with a TNFα antagonist). The Pearson's chi-square test will be also performed.

(23) Summary statistics and 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(24) Summary statistics and 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for changes from baseline in the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(25) 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 based on the analysis of covariance (ANCOVA) model with changes from baseline in the CDAI score at each visit as a response, the treatment groups in the induction phase and "prior TNFα antagonist use" as factors, and CDAI score at baseline as a covariate.

(26) The same analysis as (23) will be performed for each CDAI subscore at each visit.

(27) The same analysis as (24) will be performed for changes from baseline in each CDAI subscore at each visit.

2.3.2 Endpoints Related to CDAI Scores Based on the Hematocrit Level at Each Study Site

Analysis set: Full analysis set in the induction phase

Analysis variables:	Clinical remission	[Clinical remission, Non-remission]
	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	Durable remission	[Durable remission, Non-durable remission]
	Durable CDAI-100 response	[Durable CDAI-100 response, Non-durable CDAI-100 response]
	Durable CDAI-70 response	[Durable CDAI-70 response, Non-durable CDAI-70 response]
	CDAI score change over time	
	CDAI subscore change over time	
Visit:	Weeks 0, 2, 6, and 10	

Analysis methodology: Each analysis variable will be determined using the CDAI score based on the Ht level at each study site and CDAI subscores.

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

(1) Frequency distributions will be provided for clinical remission 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.

(2) Frequency distributions will be provided for clinical remission at each visit with stratification according to “prior TNFα 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.

(3) The CMH test using “prior TNFα antagonist use” as a stratification factor will be performed for clinical remission at

each visit 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

(4) The same analysis as (1) will be performed for the CDAI-100 response at each visit.

(5) The same analysis as (2) will be performed for CDAI-100 response at each visit with stratification according to "prior TNFα antagonist use."

(6) The same analysis as (3) will be performed for the CDAI-100 response at each visit.

(7) The same analyses as (1), (2), and (3) will be performed for the CDAI-70 response, durable remission, durable CDAI-100 response, and the durable CDAI-70 response respectively.

(8) Summary statistics and 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(9) Summary statistics and 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for changes from baseline in the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(10) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with changes from baseline in the CDAI score at each visit as a response, the treatment groups in the induction phase and "prior TNFα antagonist use" as factors, and CDAI score at baseline as a covariate.

(11) The same analysis as (8) will be performed for each CDAI subscore at each visit.

(12) The same analysis as (9) will be performed for changes from

baseline in each CDAI subscore at each visit.

2.3.3 Endpoints Related to CRP

Analysis set: Full analysis set in the induction phase

Analysis variables: CRP Level

CRP Level (within the reference range) [Yes, No]

Visit: Weeks 0, 2, 6, and 10

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 CRP level at each visit (baseline to Week 10). Summary statistics, 95% two-sided CI of the mean, 10^{th} and 90^{th} percentiles will be calculated for changes from baseline in CRP level at each visit (Week 2 to Week 10).

(2) The same analysis as (1) will be performed with stratification according to "prior TNFα antagonist use."

(3) The van Elteren test (CMH test with the modified ridit score) stratified by "prior TNFα antagonist use" will be performed for changes from baseline in CRP level at each visit (Week 2 to Week 10).

(4) In the subpopulation of subjects with the baseline CRP level outside the reference range (>0.30 mg/dL), frequency distributions will be provided for subjects with CRP level within the reference range at each visit (Week 2 to Week 10) along with the point estimate and 95% two-sided CI for the proportion. The Pearson's chi-square test will be performed to calculate the point estimate and 95% two-sided CI for the difference in the proportion between treatment groups (MLN0002 group − placebo group).

(5) The same analysis as (4) will be performed in the subpopulation of subjects with the baseline CRP level of >0.5 mg/dL.

(6) The same analysis as (4) will be performed in the subpopulation of subjects with the baseline CRP level of >1.0 mg/dL.

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

IBDQ total score ≥170 [Yes, No]

Change from baseline in IBDQ total score ≥16 [Yes, No]

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

(3) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with changes from baseline in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 10 as a response, the treatment groups in the induction phase as a factor, and

baseline 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 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 is ≥16 and subjects whose IBDQ total score change at Week 10 from baseline 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 is ≥16 and proportion of subjects whose IBDQ total score change at Week 10 from baseline 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 is ≥16 and the proportion of subjects whose IBDQ total score change at Week 10 from baseline is ≤-16 between treatment groups (MLN0002 group − placebo group) will be calculated. The Pearson's chi-square test will be also performed.

2.3.5 Analysis in Specific Subgroup 1

Analysis set:	Subjects with the baseline CRP level of >0.3 mg/dL among the full analysis set in the induction phase	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]

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

(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.

(2) Frequency distributions will be provided with stratification according to "prior TNFα 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.

(3) The CMH test using "prior TNFα antagonist use" as a stratification factor will be performed 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

2.3.6 Analysis in Specific Subgroup 2

Analysis set:	Subjects with the baseline CRP level of >0.3 mg/dL among the full analysis set in the induction phase	
Analysis variables:	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission	[Clinical remission, Non-remission]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	Durable remission	[Durable remission, Non-durable remission]
	Durable CDAI-100 response	[Durable CDAI-100 response, Non-durable CDAI-100 response]
	Durable CDAI-70 response	[Durable CDAI-70 response, Non-durable CDAI-70 response]
	CDAI score	

	CDAI subscores IBDQ scores (total score and each subscore [abdominal symptoms, general condition, emotion, and social function])
Visit:	Weeks 0, 2, 6, and 10
Analysis methodology:	The following analyses of (1), (2), and (3) will be performed for the above analysis variables except for CDAI score, CDAI subscores, and IBDQ scores by treatment group in the induction phase. The following analyses of (4), (5), and (6) will be performed for CDAI score by treatment group in the induction phase. The following analyses of (7) and (8) will be performed for CDAI subscores by treatment group in the induction phase. The following analyses of (9), (10), and (11) will be performed for IBDQ scores by treatment group in the induction phase. In addition, the analyses similar to those in section 1.2.1 will be performed. (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. (2) Frequency distributions will be provided with stratification according to "prior TNFα 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. (3) The CMH test using "prior TNFα antagonist use" as a stratification factor will be performed 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated. (4) Summary statistics and 95% two-sided CI of the mean will be

provided for the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(5) Summary statistics and 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for changes from baseline in the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(6) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with changes from baseline in the CDAI score at each visit as a response, the treatment groups in the induction phase and "prior TNFα antagonist use" as factors, and CDAI score at baseline as a covariate.

(7) The same analysis as (4) will be performed for each CDAI subscore at each visit.

(8) The same analysis as (5) will be performed for changes from baseline in each CDAI subscore at each visit.

(9) 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.

(10) Summary statistics and 95% two-sided CI of the mean will be calculated for changes from baseline in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 10.

(11) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with changes from baseline in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 10 as a response, the treatment groups in the induction phase as a factor, and baseline values that correspond to the scores used as response

as a covariate.

2.3.7 Combinational Analysis of CDAI Score and CRP Level

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	CRP level of ≤1.6 mg/dL at Week 10	[Yes, No]
	CDAI-100 response at Week 10 with CRP level of ≤1.6 mg/dL at Week 10	[Yes, No]
	Clinical remission at Week 10 with CRP level of ≤1.6 mg/dL at Week 10	[Yes, No]

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

(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.

(2) Frequency distributions will be provided with stratification according to "prior TNFα 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.

(3) The CMH test using "prior TNFα antagonist use" as a stratification factor will be performed 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

2.4 Statistical and Analytical Issues

2.4.1 Adjustments for Covariates

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]

	Clinical remission at Week 10	[Clinical remission, Non-remission]
Adjustment factors:	Prior TNFα antagonist use	[Yes, No]
	Age (years)	[Min≤ - ≤34, 35≤ - ≤Max]
	Concomitant use of 5-ASA at baseline	[Yes, No]
	Concomitant use of immunomodulators at baseline	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	CDAI score at baseline	[Min≤ - ≤330, 330< - ≤Max]
Analysis methodology:	Influences of the above adjustment factors on odds ratios for the CDAI-100 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 the CDAI-100 response at Week 10 and clinical remission at Week 10 after adjusting the influence of stratification factors will be investigated. In addition, interactions between treatment and adjustment factors will be investigated using the Breslow-Day test.	

2.4.2 Handling of Dropouts or Missing Data

The efficacy endpoints of clinical response and clinical remission will be considered as non-response or non-remission 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.

2.4.3 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.

2.4.4 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.

2.4.5 Multiple Comparisons/Multiplicity

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 the CDAI-100 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 10% 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.

2.4.6 Use of an "Efficacy Subset of Subjects"

To confirm the robustness of the primary analysis results for the primary endpoint from 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."

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

Not applicable.

2.4.8 Examination of Subgroups

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 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 CD (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 enteral nutrient at baseline	[Yes, No]
Concomitant use of 5-ASA at baseline	[Yes, No]
Concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids at baseline	[Yes, No]
No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline	[Yes, No]

	(concomitant use of immunomodulators only)	
	Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline	[Yes, No]
	CDAI score at baseline	[Min≤ - <330, 330≤ - ≤Max]
	Disease localization	[Small intestinal, Large intestinal, Small/Large intestinal]
	Weight (kg) at baseline	[Min≤ - ≤59.9, 60.0≤ - ≤Max]
	CRP (mg/dL) at baseline	[Min≤ - ≤0.3, 0.3< - ≤Max]
		[Min≤ - ≤0.5, 0.5< - ≤Max]
		[Min≤ - ≤1.0, 1.0< - ≤Max]
		[Min≤ - ≤1.6, 1.6< - ≤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.

(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 treatment group in the induction phase.

(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 the induction phase (time)	[1, 2, 3]

Analysis methodology: The following summaries will be provided for the above analysis variables using frequency distributions by treatment group in the induction phase.

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 (time) 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 (time) by SOC and PT

(15) TEAEs in the induction phase whose incidence summarized by PT is 3% or higher in either treatment 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 TEAEs 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 a TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages of TEAEs 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 TEAEs 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 a 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 (time) by SOC and PT"

  A subject with a TEAE that occurs in more than one time of the study drug administration is counted for all the administrations (time) that the TEAE occurs. For each administration, a subject with multiple occurrences of a TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages of TEAEs 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 the 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 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	

Categories: Adjudication results based on 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, 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 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 the 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 baseline and each post-baseline visit
(4) Shift tables showing categories of SAP Appendix 2 (1) at baseline 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 range [Below lower limit of normal range, Within normal range, Over upper limit of normal range]
Visit:	Weeks 0, 10, 14, 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 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 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 the differences before and after administration
(2) Case plots
(3) Shift tables showing adjudication results based on normal reference range at baseline 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 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, 10, and 16 weeks after the last dose of the study drug

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

ECG by 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 baseline 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:	Summaries similar to those in section 3.1.2 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 induction phase"
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. When calculating the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV% (2) Mean/standard deviation plot

4.2 Subgroup 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 induction phase"	
Analysis variables:	Serum concentrations of MLN0002	
Stratum:	Prior TNFα antagonist use	[Yes, No]
	Concomitant use of 5-ASA at baseline	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	Concomitant use of immunomodulators at baseline	[Yes, No]
Visit:	Weeks 2, 6, 10, and 14	
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum. When calculating the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV%	

4.3 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 induction phase"	
Analysis variables:	Serum concentrations of MLN0002	
Stratum:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]

	Clinical remission at Week 10	[Clinical remission, Non-remission]
Visit:	Weeks 2, 6, 10, and 14	
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum. When calculating the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV%	

4.4 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 induction phase"	
Analysis variables:	Serum concentrations of MLN0002	
Stratum:	AVA at Week 10	[Negative, Positive]
	Neutralizing antibody at Week 10	[Negative, Positive]
	AVA in the induction phase	[Negative, Positive]
	Neutralizing antibody in the induction phase	[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. When calculating the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV%	

4.5 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 induction phase"	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
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]

Analysis methodology: The following analysis will be performed for the above analysis variables for each stratum. 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 the Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and the neutralizing antibody in the "full analysis set in the induction phase"	
Analysis variables:	AVA	[Negative, Positive]
	AVA titer	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Neutralizing antibody	[Negative, Positive]
	AVA in the induction phase	[Negative, Positive]
	Maximum AVA titer in the induction phase	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Neutralizing antibody in the induction phase	[Negative, Positive]
Visit:	Weeks 0, 10, 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 defined 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 the Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and the neutralizing antibody in the "full analysis set in the induction phase"	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
Stratum:	AVA at Week 10	[Negative, Positive]
	Neutralizing antibody at Week 10	[Negative, Positive]
	AVA in the induction phase	[Negative, Positive]

	Neutralizing antibody in the induction phase	[Negative, Positive]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum. (1) Frequency distributions	

5.3 Subgroup Analysis of AVA and the Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and the neutralizing antibody in the "full analysis set in the induction phase"	
Analysis variables:	AVA	[Negative, Positive]
	Neutralizing antibody	[Negative, Positive]
	AVA in the induction phase	[Negative, Positive]
	Neutralizing antibody in the induction phase	[Negative, Positive]
Stratum:	Concomitant use of immunomodulators at baseline	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	Infusion reactions in the induction phase	[Yes, No]
Visit:	Weeks 0, 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. 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 of the CMH test in 2.1.1, 2.1.2 (1), 2.2(3), and 2.4.1: 10% (two-sided test)
- Significance level of other tests: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided estimate)

History of Revision (version management)

Version	Date	Prepared/modified by	Comments
First version	25 January 2018	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 and 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 ($\times 10^4$/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 criterion, 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

Label	Criteria for "elevated liver enzyme"	
	Elevated	Not elevated
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	Both ALP and ALT are greater than 3	Either ALP is non-missing and less than

Label	Criteria for “elevated liver enzyme”	
	Elevated	Not elevated
with ALT > 3×ULN	time the ULN	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.

ADDITIONAL 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 Crohn's disease
Protocol No.	: MLN0002/CCT-001
Sponsor	: Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

PPD

Trial Statistician

PPD

First version: 12 April 2018

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The same methods of summaries and handling as those in the Statistical Analysis Plan (Induction Phase) for Study CCT-001 will be applied, unless otherwise stated.

1 EFFICACY ANALYSIS

1.1 Analysis in Specific Subgroup

Analysis set:	Subjects with the baseline CRP level of >1.6 mg/dL among the full analysis set in the induction phase	
Analysis variables:	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission	[Clinical remission, Non-remission]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	Durable remission	[Durable remission, Non-durable remission]
	Durable CDAI-100 response	[Durable CDAI-100 response, Non-durable CDAI-100 response]
	Durable CDAI-70 response	[Durable CDAI-70 response, Non-durable CDAI-70 response]
	CDAI score	
Visit:	Weeks 0, 2, 6, and 10	

Analysis methodology: The following analyses of (1), (2), and (3) will be performed for the above analysis variables except for CDAI score by treatment group in the induction phase. The following analyses of (4), (5), and (6) will be performed for CDAI score by treatment group in the induction phase.

(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.

(2) Frequency distributions will be provided with stratification according to “prior TNFα 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.

(3) The Cochran-Mantel-Haenszel (CMH) test using "prior TNFα antagonist use" as a stratification factor will be performed 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

(4) Summary statistics and 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(5) Summary statistics and 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time. Summary statistics and 95% two-sided CI of the mean will be calculated for changes from baseline in the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(6) 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 based on the analysis of covariance (ANCOVA) model with changes from baseline in the CDAI score at each visit as a response, the treatment groups in the induction phase and "prior TNFα antagonist use" as factors, and CDAI score at baseline as a covariate.

1.2 Combinational Analysis of CDAI Score and CRP Level in Specific Subgroup

Analysis set:	Subjects with the baseline CRP level of >1.6 mg/dL among the full analysis set in the induction phase	
Analysis variables:	CRP level of ≤1.6 mg/dL	[Yes, No]
	CDAI-100 response with CRP level of ≤1.6 mg/dL	[Yes, No]
	Clinical remission with CRP level of ≤1.6 mg/dL	[Yes, No]
Visit:	Weeks 0, 2, 6, and 10	

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

(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.

(2) Frequency distributions will be provided with stratification according to "prior TNFα 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.

(3) The CMH test using "prior TNFα antagonist use" as a stratification factor will be performed 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 "prior TNFα antagonist use" as a stratification factor and the 95% two-sided CI will be calculated.

1.3 Adjustments for Covariates

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
Adjustment factors:	Disease localization	[Small intestinal, Large intestinal, Small/Large intestinal]
		[Small intestinal or Large intestinal, Small/Large intestinal]

Analysis methodology: Influences of the above adjustment factors on odds ratios for the CDAI-100 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 the CDAI-100 response at Week 10 and clinical remission at Week 10 after adjusting the influence of stratification factors will be investigated. In addition, interactions between treatment and adjustment factors will be investigated using the Breslow-Day test.

1.4 Examination of Subgroups

Analysis set:	Full analysis set in the induction phase	
Analysis variables:	CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]
	Clinical remission at Week 10	[Clinical remission, Non-remission]
Stratum:	Disease localization	[Small intestinal or Large intestinal, Small/Large intestinal]

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.

(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.

2 SIGNIFICANCE LEVEL AND CONFIDENCE COEFFICIENT

- Significance level of the CMH test in 1.3: 10% (two-sided test)
- Significance level of other tests: 5% (two-sided test)
- Confidence coefficient: 95% (two-sided estimate)

History of Revision (version management)

Version	Date	Prepared/modified by	Comments
First version	12 April 2018	PPD	Preparation of first version

[Appendix 1] Comparison Table for Changes

N/A

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 Crohn's disease

Protocol No. : MLN0002/CCT-001

Sponsor : Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

PPD

Trial Statistician

PPD

Person responsible for pharmacokinetic/pharmacodynamic analyses

PPD

First version: 25 January 2018

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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 CDAI-70 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 induction phase: MLN0002 group and placebo group.
- 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.

- CDAI-70 responders at Week 10: Subjects who were determined to have achieved CDAI-70 response at Week 10 on the website of the registration center.
- Baseline: A visit at "Week 0" in the "HANDLING OF TIME WINDOW"

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 evaluable 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.

CDAI score*[1], each CDAI subscore*[2] (both based on the hematocrit [Ht] level at each study site)

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*[3]	Study Day: 43	29 to 56	
Week 10*[4]	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	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 58	Study Day: 407	393 to 413	
Week 60*[5]	Study Day: 421	414 to 448	
Week 60 (LOCF)*[6]			

*[1] CDAI-70 response, CDAI-100 response, and clinical remission will be determined by using both CDAI score based on the Ht level at each study site and CDAI score based on the Ht level at the central laboratory, respectively.

*[2] Each CDAI subscore used for the calculation of CDAI scores based on the Ht level at each study site will be used.

*[3] If the CDAI subscore (7) at Week 6 is missing, the same CDAI subscore (7) as that obtained at Week 2 will be used for Week 6.

*[4] If the CDAI subscore (7) at Week 10 is missing, the same CDAI subscore (7) as that obtained at Week 6 will be used for Week 10. However, if the CDAI subscore (7) at Week 2 is used for Week 6 according to the handling described in *3, the CDAI subscore (7) at Week 10 will be handled as missing.

*[5] If the CDAI subscore (7) at Week 60 is missing, the same CDAI subscore (7) as that obtained at Week 58 will be used for Week 60. If the CDAI score at Week 60 is missing, the same CDAI score as that obtained at Week 58 will be used for Week 60.

*[6] 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.

Ht level*[1] (tested by the central laboratory), inflammatory marker (CRP)

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*[2]	Study Day: 43	29 to 56	
Week 10*[3]	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	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
Week 60	Study Day: 421	400 to 448	
Week 60 (LOCF)*[4]			

*[1] The Ht level will be handled as follows:

- If the Ht level tested on the same date as the evaluation day of the CDAI score based on the Ht level at each study site is available, that Ht level will be used.
- If the Ht level tested on the same date as the evaluation day of the CDAI score based on the Ht level at each study site is not available, it will be handled according to the general rules described directly beneath the "HANDLING OF TIME WINDOW."

*[2] If the Ht level at Week 6 is missing, the same Ht level as that obtained at Week 2 will be used for Week 6.

*[3] If the Ht level at Week 10 is missing, the same Ht level as that obtained at Week 6 will be used for Week 10. However, if the Ht level at Week 2 is used for Week 6 according to the handling described in *2, the Ht level at Week 10 will be handled as missing.

*[4] 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)

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.

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	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
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	
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	414 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 (days): 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 (days): 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 CD (years): (Date of informed consent [year and month] − Date of CD diagnosis [year and month]) / 12 (round off to the first decimal place)
  - Only the year and month for the date of informed consent will be used.
  - The unit for "Date of informed consent (year and month) − Date of CD diagnosis (year and month)" will be "months."
  - If the year of CD diagnosis is unknown, the duration of CD will be handled as "Missing." If only the month of CD diagnosis is unknown, the duration of CD will be calculated by setting the month of CD diagnosis as January.
- Prior corticosteroids failure: If corticosteroid 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 corticosteroids failure is "Yes" are classified as follows:
  - Subjects for whom corticosteroid resistance is "Yes" are classified as "Resistance."
  - Among subjects for whom corticosteroid resistance is not "Yes," subjects for whom corticosteroid dependence is "Yes" are classified as "Dependence."

  - Among subjects for whom corticosteroid 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 corticosteroids 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 corticosteroid 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 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 is not "Yes," subjects for whom immunomodulatory intolerance is "Yes" are classified as "Intolerance."
- Prior TNFα antagonist failure: If inadequate response, loss of response, or intolerance to the TNFα antagonist is "Yes," prior TNFα antagonist failure will be defined as "Yes." Any response other than the above will be defined as "No."
- Number of drugs of TNFα antagonist failure: Among the drugs entered to prior treatment failure (TNFα antagonist) for CD, 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 (TNFα antagonist) for CD are classified as "None."
- Classification of prior TNFα antagonist failure: Subjects for whom prior TNFα antagonist failure is "Yes" are classified as follows:
  - Subjects for whom TNFα antagonist inadequate response is "Yes" are classified as "Inadequate response."
  - Among subjects for whom TNFα antagonist inadequate response is not "Yes," subjects for whom TNFα antagonist loss of response is "Yes" are classified as "Loss of response."
  - Among subjects for whom TNFα antagonist inadequate response is not "Yes" as well as TNFα antagonist loss of response not being "Yes," subjects for whom TNFα antagonist intolerance is "Yes" are classified as "Intolerance."
- Prior immunomodulators failure (excluding prior TNFα antagonist failure): If prior TNFα antagonist failure is "No" and prior immunomodulators failure is "Yes," prior immunomodulators failure (excluding prior TNFα antagonist failure) will be defined as "Yes." All others will be defined as "No."
- Prior corticosteroids failure only: If prior TNFα antagonist failure is "No," prior immunomodulators failure is "No," and prior corticosteroids failure is "Yes," prior corticosteroids failure only will be defined as "Yes." All others will be defined as "No."
- Prior immunomodulators and TNFα antagonist failure: If prior immunomodulators failure is "Yes" and prior TNFα antagonist failure is "Yes," prior immunomodulators and TNFα 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 ≥75%), the study drug infusion will be defined as "Completed." All others will be defined as "Incompleted."

The Ht level and CDAI score will be handled as follows:

- The CDAI score, CDAI subscore, and Ht levels used for analysis will be determined at the central laboratory unless otherwise noted.
- CDAI score: The sum of CDAI subscores of (1) to (8) defined in the table below.

(1)	Number of liquid or very soft stools during the last 1 week	× 2
(2)	Abdominal pain during the last 1 week (7-day total of daily abdominal pain scores on a following scale) 0=None, 1=Mild, 2=Moderate, 3=Severe	× 5
(3)	Subjective general well being during the last 1 week (7-day total of daily general well-being scores on a following scale) 0=Generally well, 1=Slightly under par, 2=Poor, 3=Very poor, 4=Terrible	× 7
(4)	Current number of the following extraintestinal manifestations of CD 1) Arthritis/arthralgia 2) Iritis/uveitis 3) Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis 4) Anal fissure, anal fistula, or perianal abscess 5) Other fistula 6) Fever over 37.8°C during the last 1 week	× 20
(5)	Use of antidiarrheal drugs (e.g., lopemin) or opiates for diarrhea 0=No, 1=Yes	× 30
(6)	Abdominal mass 0=None, 2=Questionable, 5=Definite	× 10
(7)	Hematocrit (%)[Note 1)] Males: subtract value from 47, Females: subtract value from 42	× 6
(8)	Body weight : Standard weight (body-weight ratio)[Note 2)] [1 − (Body weight / Standard weight)] × 100	× 1

Note 1) If hematocrit subtotal <0, enter 0.

Note 2) If body weight subtotal <-10, enter -10.

- The CDAI score will be calculated using subscores on the same day of evaluation. For subscore (7), however, the CDAI score will be calculated using the Ht level obtained within the same visit window if the Ht level on the same day of evaluation is not available.
- If any CDAI subscore is missing, the CDAI score will be handled as missing.
- CDAI-70 response: Subjects will be classified as "CDAI-70 response" if "a ≥70-point decrease in CDAI score from baseline" is achieved. All others will be classified as "Non-CDAI-70 response." However, if any CDAI score change 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 the "HANDLING OF TIME WINDOW," subjects will be classified as "Non-CDAI-70 response."
- CDAI-100 response: Subjects will be classified as "CDAI-100 response" if "a ≥100-point decrease in CDAI score from baseline" is achieved. All others will be classified as

"Non-CDAI-100 response." However, if any CDAI score change 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 the "HANDLING OF TIME WINDOW," subjects will be classified as "Non-CDAI-100 response."

- Clinical remission: Subjects will be classified as "Clinical remission" if a "CDAI score of ≤150" is achieved. All others will be classified as "Non-remission." However, if any of the CDAI scores 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 the "HANDLING OF TIME WINDOW," subjects will be classified as "Non-remission."

After the CDAI-70 response, CDAI-100 response, and clinical remission at each visit are determined using the above methods, the following durable CDAI-70 response in the maintenance phase, durable CDAI-100 response in the maintenance phase, and durable remission in the maintenance phase will be determined.

- Durable CDAI-70 response in the maintenance phase: If "CDAI-70 response" is observed at ≥80% of visits after Week 10 except Week 60 (LOCF), subjects will be classified as "Durable CDAI-70 response." All others will be classified as "Non-durable CDAI-70 response."
- Durable CDAI-100 response in the maintenance phase: If "CDAI-100 response" is observed at ≥80% of visits after Week 10 except Week 60 (LOCF), subjects will be classified as "Durable CDAI-100 response." All others will be classified as "Non-durable CDAI-100 response."
- Durable remission in the maintenance phase: If "Clinical remission" is observed at ≥80% of visits after Week 10 except Week 60 (LOCF), subjects will be classified as "Durable remission." All others will be classified as "Non-durable remission."
  - For CDAI scores based on the Ht level at the central laboratory, "≥80% of visits after Week 10" will be defined as "7 or more out of 8 visits (Weeks 10, 14, 22, 30, 38, 46, 54, and 60)."
  - For CDAI scores based on the Ht level at each study site, "≥80% of visits after Week 10" will be defined as "12 or more out of 14 visits (Weeks 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, and 60)."

- Disease worsening: All CDAI 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 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, and all CDAI 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:
  - If the CDAI scores based on the Ht level at the central laboratory increase by ≥100 points from that of Week 10 and become ≥220 points on 2 consecutive visits by confirming them in ascending order of visit date, subjects will be classified as "Yes" for disease worsening based on the Ht level at the central laboratory. The onset date of disease worsening based on the Ht level at the central laboratory will be defined as the earlier date of these visits, after excluding missing values.
  - The disease worsening based on the Ht level at each study site will be determined in the same manner as above using the CDAI scores based on the Ht level at each study site and the onset date of disease worsening based on the Ht level at each study site will be specified.
  - A subject for whom disease worsening based on the Ht level at the central laboratory was

determined to be “Yes” or disease worsening based on the Ht level at each study site was determined to be “Yes” will be defined as “Yes” for disease worsening.

- The onset date of disease worsening will be defined as the earlier date on which either the onset of disease worsening based on the Ht level at the central laboratory or the onset of disease worsening based on the Ht level at each study site was observed.
- 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 CDAI score – Date of the first dose of the study drug in the maintenance phase + 1” will be used for analysis.

- Rescue treatments: All concomitant medications (for treatment of CD) 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 CD) 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 a 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 events, and the onset date of discontinuation due to the 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 above events, 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 the 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.

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	• 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 the calculation of that subscore. • If 2 questions are missing among those used for the calculation of each subscore, that subscore will be handled as missing.
IBDQ total score	• Among the questions used for the calculation of IBDQ total score, the missing data will be imputed using the mean of the non-missing questions used for the calculation of each subscore. However, if 5 or more questions are missing or 2 or more subscores are missing among the questions used for the 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 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 in IBDQ total score: "Yes" if the change from baseline 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."

Prior TNFα antagonist use, concomitant use of immunomodulators at baseline, and concomitant use of oral corticosteroids at baseline will be defined as follows:

- Prior TNFα 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 baseline: Subjects who received any concomitant medication (for treatment of CD) which is classified as "immunomodulator" in the concomitant medication (for treatment of CD) 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 CD) 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 baseline: Subjects who received any concomitant medication (for treatment of CD) which is classified as "corticosteroid" and whose route of administration is "oral" in the concomitant medication (for treatment of CD) 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 CD) 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."

Concurrent extraintestinal manifestations (based on CDAI subscore [4]), concurrent extraintestinal manifestations (based on case report form [CRF] concurrent medical condition section), surgical history for CD, medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent, and concurrent medical condition related to fistula will be defined as follows:

- Concurrent extraintestinal manifestations (based on CDAI subscore [4]): Subjects whose CDAI

subscore [4] at baseline is greater than 0 will be classified as “Yes.” All others will be classified as “No.”

- Concurrent extraintestinal manifestations (based on CRF concurrent medical condition section): Subjects recorded to have concurrent extraintestinal manifestations of CD in the CRF concurrent medical condition section will be classified as “Yes.” All others will be classified as “No.”
- Surgical history for CD: Subjects coded with at least one PT in the following table for medical history will be classified as “Yes.” All others will be classified as “No.”

Preferred Term
Anal skin tag excision
Colectomy
Crohn's disease
Enterocutaneous fistula
Ileal operation
Ileectomy
Ileocolectomy
Ileocolostomy
Ileostomy
Ileostomy closure
Intestinal resection
Proctectomy
Sigmoidectomy
Small intestinal resection
Small intestine operation
Stricturoplasty
Urinary cystectomy

- Medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent: Subjects coded with at least one PT in the following table for medical history or concurrent medical condition will be classified as “Yes.” All others will be classified as “No.”

Medical history

Preferred Term
Anal fistula
Fistula of small intestine

Concurrent medical condition

Preferred Term
Anal fistula
Enterocutaneous fistula
Female genital tract fistula

- Concurrent medical condition related to fistula: Subjects coded with at least one PT in the

following table for concurrent medical condition will be classified as “Yes.” All others will be classified as “No.”

Preferred Term
Anal fistula
Enterocutaneous fistula
Female genital tract fistula

Among concomitant medications (for treatment of CD) in the maintenance phase, the medication which is classified as “corticosteroid” 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	
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)			

- Oral corticosteroid dosage at each visit other than Week 60 (LOCF): Oral corticosteroid dosage for each Study Day period will be defined as the sum of daily doses of oral corticosteroids (converted dosage of prednisolone) used for each Study Day period. For the Study Day period when oral corticosteroids are not used, the daily dose will be "0." Oral corticosteroid dosage at each visit will be the mean of oral corticosteroid dosage for 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 baseline 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 the "HANDLING OF TIME WINDOW" will be used.

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. The neutralizing antibody will be handled as missing if it does not correspond to any of the above.

After determining the negative or positive status of the neutralizing antibody at each visit with the above-mentioned logic, the following determination will be made:
- AVA in the induction and maintenance phases
  - Subjects in the induction and maintenance phases 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 in the induction and maintenance phases 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.
- Persistently positive in the induction and maintenance phases
  - "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" will be classified as persistently positive.
- Transiently positive in the induction and maintenance phases
  - 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 were 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.

- Neutralizing antibody in the induction and maintenance phases
  - Subjects in the induction and maintenance phases 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 in the induction and maintenance phases 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:

- Lymphocytes = WBC × lymphocytes (%)
- Neutrophils = WBC × 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 last visit or contact in the maintenance phase, whichever comes later
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 Maintenance Phase

Analysis set: All subjects who achieved CDAI-70 response at Week 10 and did not enter in the maintenance 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 by each treatment group in the induction phase and in the consolidated 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 CDAI-70 response at Week 10

Analysis variables: Eligibility for entering into the maintenance phase [Eligible, Not eligible]

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

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 the 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 the percentages of the reasons for not being completed, the number of subjects who did not complete 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 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]
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: 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 distribution of subjects with protocol deviations in the maintenance phase will be provided for each deviation category above. 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 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 the analysis set
(2) Frequency distributions concerning the handling of subject data in the maintenance phase in the analysis set
(3) Frequency distributions concerning the number of subjects included in the 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 baseline	[Min≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
BMI (kg/m^2) at baseline	[Min≤ - ≤18.4, 18.5≤ - ≤24.9, 25.0≤ - ≤Max]
Smoking classification	[Never smoked, Current smoker, Ex-smoker]
Duration of CD (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 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 corticosteroids failure only]
Prior immunomodulators and TNFα antagonist failure	[Yes, No]
Prior TNFα antagonist use	[Yes, No]
Infliximab	[Yes, No]
Adalimumab	[Yes, No]
Golimumab	[Yes, No]
Concomitant use of enteral nutrient at baseline	[Yes, No]
Concomitant use of 5-ASA at baseline	[Yes, No]
Concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids at baseline	[Yes, No]
No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline	[Yes, No]
CDAI score at baseline	[Min≤ - ≤220, 220< - ≤330, 330< - ≤450, 450< - ≤Max]
CDAI score at Week 10	[Min≤ - ≤150, 150< - ≤220, 220< - ≤330, 330< - ≤450, 450< - ≤Max]
CDAI-70 response at Week 10	[CDAI-70 response, Non-CDAI-70 response]
CDAI-100 response at Week 10	[CDAI-100 response, Non-CDAI-100 response]

Clinical remission at Week 10	[Clinical remission, Non-remission]
CDAI subscore (1): Number of liquid or very soft stools during the last 1 week at baseline CDAI subscore (2): Abdominal pain during the last 1 week at baseline CDAI subscore (3): Subjective general well being during the last 1 week at baseline CDAI subscore (4): Current number of extraintestinal manifestations of CD (e.g., arthritis/arthralgia) at baseline	[0, 1, 2, 3, 4, 5, 6]
CDAI subscore (5): Use of antidiarrheal drugs (e.g., lopemin) or opiates for diarrhea at baseline	[No, Yes]
CDAI subscore (6): Abdominal mass at baseline	[None, Questionable, Definite]
CDAI subscore (7): Hematocrit level at baseline CDAI subscore (8): Body weight : Standard weight (body-weight ratio) at baseline	
Disease localization	[Small intestinal, Large intestinal, Small/Large intestinal]
Concurrent extraintestinal manifestations (based on CDAI subscore [4])	[Yes, No]
Concurrent extraintestinal manifestations (based on CRF concurrent medical condition section)	[Yes, No]
CRP (mg/dL) at baseline	[Min≤ - ≤0.3, 0.3< - ≤0.5, 0.5< - ≤1.0, 1.0< - ≤1.6, 1.6< - ≤Max]
Surgical history for CD	[Yes, No]
Medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent	[Yes, No]
Concurrent medical condition related to fistula	[Yes, No]
Number of the study drug infusions in the induction phase	[1, 2, 3]

	Clinical remission at Week 10 (based on the CDAI scores calculated using the Ht level at each study site)	[Clinical remission, Non-remission]
	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." The similar analysis will be performed with stratification according to "prior TNFα antagonist use."

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

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 CD) (by SOC and PT)
(3) Frequency distributions for concurrent medical conditions (other than concurrent extraintestinal manifestations of CD) (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 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 CD) in the maintenance phase	
	Classification of concomitant medications (for treatment of CD) in the maintenance phase	[5-ASA, Corticosteroids, Immunomodulators, Enteral nutrients, Other]
	Concomitant medications (for treatment of CD) in the maintenance phase that fall under the category of rescue treatments	
	Classification of concomitant medications (for treatment of CD) in the maintenance phase that fall under the category of rescue treatments	[5-ASA, Corticosteroids, Immunomodulators, Enteral nutrients, Other]
	Concomitant medications (for other than treatment of CD) in the maintenance phase	
	Concomitant therapies in the maintenance phase	[Yes, No]
	Concomitant therapies in the maintenance 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 "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 CD) in the maintenance phase, concomitant medications (for treatment of CD) in the maintenance phase that fall under the category of rescue treatments, and concomitant medications (for other than treatment of CD) 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 CD) 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 CD) 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 CD) 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 CD) 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 CD) 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 CD) 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 incompleted 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 incompleted infusions will be counted as frequency for "Incompleted." When calculating the percentage, the sum of the number of completed infusions and the number of incompleted 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. From 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 TNFα 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 TNFα antagonist use." The Pearson's chi-square test will be performed to calculate the odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI for reference.	

2.1.2 Secondary Analysis

Analysis set:	Per protocol set in the maintenance phase	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
Stratum:	Prior TNFα antagonist use	[Yes, No]
Analysis methodology:	From sensitivity point of view, the following analysis will be performed to examine the robustness of the results. (1) The clinical remission at Week 60 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."	

2.2 Secondary Endpoints and Analysis Methodology

Analysis set:	Full analysis set in the maintenance phase Subjects who were receiving oral corticosteroids concomitantly at baseline in the full analysis set in the maintenance phase	
Analysis variables:	CDAI-100 response at Week 60	[CDAI-100 response, Non-CDAI-100 response]
	Durable remission in the maintenance phase	[Durable remission, Non-durable remission]

	Corticosteroid-free remission at Week 60	[Corticosteroid-free remission, Non-corticosteroid-free remission]
Stratum:	Prior TNFα antagonist use	[Yes, No]

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

Corticosteroid-free remission at Week 60 will be analyzed in "subjects who were receiving corticosteroids concomitantly at baseline in the full analysis set in the maintenance phase." All other variables will be analyzed in the "full analysis set in the maintenance phase."

(1) Frequency distributions will be provided for each analysis variable 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 each analysis variable with stratification according to "prior TNFα 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.

(3) The Pearson's chi-square test will be performed to calculate the 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 CDAI Scores

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	Clinical remission	[Clinical remission, Non-remission]
	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	Durable CDAI-100 response in the maintenance phase	[Durable CDAI-100 response, Non-durable CDAI-100 response]
	Durable CDAI-70 response in the maintenance phase	[Durable CDAI-70 response, Non-durable CDAI-70 response]
	Clinical remission at Week 60 in the subpopulation of subjects without prior	[Clinical remission, Non-remission]

	TNFα antagonist use and in the subpopulation of subjects who failed with a TNFα antagonist	
	Clinical remission at Week 60 in the subpopulation of subjects who failed with a corticosteroid monotherapy and an immunomodulator (except those failed with a TNFα antagonist)	[Clinical remission, Non-remission]
	CDAI score change over time	
	Each CDAI subscore change over time	
	Change from Week 10 in CDAI score over time	
	Change from Week 10 in each CDAI subscore over time	
Visit:	Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, and 60 (clinical remission, CDAI-100 response, and CDAI-70 response) Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 60, and Week 60 (LOCF) (CDAI score and each CDAI subscore) Week 60 (durable CDAI-100 response in the maintenance phase and durable CDAI-70 response in the maintenance phase) Weeks 2, 6, 10, 14, 22, 30, 38, 46, 54, 60, and Week 60 (LOCF) (change from baseline in CDAI score and change from baseline in each CDAI subscore) Weeks 14, 22, 30, 38, 46, 54, 60, and Week 60 (LOCF) (change from Week 10 in CDAI score and change from Week 10 in each CDAI subscore)	
Analysis methodology:	The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase. (1) Frequency distributions will be provided for clinical remission 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. (2) Frequency distributions will be provided for clinical remission at each visit with stratification according to "prior TNFα 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. (3) The Pearson's chi-square test will be performed for clinical remission at each visit to calculate the odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. (4) The same analysis as (1) will be performed for the CDAI-100 response at each visit. (5) The same analysis as (2) will be performed for CDAI-100	

response at each visit with stratification according to "prior TNFα antagonist use."

(6) The same analysis as (3) will be performed for the CDAI-100 response at each visit.

(7) The same analysis as (1) will be performed for the CDAI-70 response at each visit.

(8) The same analysis as (2) will be performed for CDAI-70 response at each visit with stratification according to "prior TNFα antagonist use."

(9) The same analysis as (3) will be performed for the CDAI-70 response at each visit.

(10) The same analysis as (1) will be performed for the durable CDAI-100 response in the maintenance phase.

(11) The same analysis as (2) will be performed for the durable CDAI-100 response in the maintenance phase with stratification according to "prior TNFα antagonist use."

(12) The same analysis as (3) will be performed for the durable CDAI-100 response in the maintenance phase.

(13) The same analysis as (1) will be performed for the durable CDAI-70 response in the maintenance phase.

(14) The same analysis as (2) will be performed for the durable CDAI-70 response in the maintenance phase with stratification according to "prior TNFα antagonist use."

(15) The same analysis as (3) will be performed for the durable CDAI-70 response in the maintenance phase.

(16) The same analysis as (1) will be performed for clinical remission at each visit in the subpopulation of subjects without prior TNFα antagonist use.

(17) The same analysis as (1) will be performed for clinical remission at each visit in the subpopulation of subjects who failed with a TNFα antagonist.

(18) The same analysis as (1) will be performed for clinical remission at each visit in the subpopulation of subjects who failed with a corticosteroid monotherapy.

(19) The same analysis as (1) will be performed for clinical remission at each visit in the subpopulation of subjects who failed with an immunomodulator (except those failed with a TNFα antagonist).

(20) Summary statistics and the 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time. Summary statistics and the 95% two-sided CI of the mean will be calculated for the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(21) Summary statistics and the 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time. Summary statistics and the 95% two-sided CI of the mean will be calculated for

changes from baseline in the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(22) 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 based on the analysis of covariance (ANCOVA) model with change from baseline in the CDAI score at Week 60 (LOCF) as a response, the treatment group in the maintenance phase as a factor, and CDAI score at baseline as a covariate.

(23) The same analysis as (20) will be performed for each CDAI subscore at each visit.

(24) The same analysis as (21) will be performed for changes from baseline in each CDAI subscore at each visit.

(25) The same analysis as (21) will be performed for changes from Week 10 in CDAI score at each visit.

(26) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with change from Week 10 in the CDAI score at Week 60 (LOCF) as a response, the treatment group in the maintenance phase as a factor, and CDAI score at Week 10 as a covariate.

(27) The same analysis as (21) will be performed for changes from Week 10 in each CDAI subscore at each visit.

2.3.2 Endpoints Related to CDAI Scores Based on the Hematocrit Level at Each Study Site

Analysis set:	Full analysis set in the maintenance phase	
Analysis variables:	Clinical remission	[Clinical remission, Non-remission]
	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	Durable remission in the maintenance phase	[Durable remission, Non-durable remission]
	Durable CDAI-100 response in the maintenance phase	[Durable CDAI-100 response, Non-durable CDAI-100 response]
	Durable CDAI-70 response in the maintenance phase	[Durable CDAI-70 response, Non-durable CDAI-70 response]
	CDAI score change over time	

	Each CDAI subscore change over time
Visit:	Weeks 0, 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, and 60 (clinical remission, CDAI-100 response, and CDAI-70 response) Weeks 0, 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60 (LOCF) (CDAI score and each CDAI subscore) Weeks 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 60, and Week 60 (LOCF) (change from baseline in CDAI score, change from baseline in each CDAI subscore) Week 60 (durable remission in the maintenance phase, durable CDAI-100 response in the maintenance phase, and durable CDAI-70 response in the maintenance phase)
Analysis methodology:	Each analysis variable will be determined using the CDAI score based on the Ht level at each study site and CDAI subscores. The following analysis will be performed for the above analysis variables by treatment group in the maintenance phase. (1) Frequency distributions will be provided for clinical remission 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. (2) Frequency distributions will be provided for clinical remission at each visit with stratification according to "prior TNFα 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. (3) The Pearson's chi-square test will be performed for clinical remission at each visit to calculate the odds ratio of the MLN0002 group to the placebo group (MLN0002 group/placebo group) and the 95% two-sided CI. (4) The same analysis as (1) will be performed for the CDAI-100 response at each visit. (5) The same analysis as (2) will be performed for CDAI-100 response at each visit with stratification according to "prior TNFα antagonist use." (6) The same analysis as (3) will be performed for the CDAI-100 response at each visit. (7) The same analyses as (1), (2), and (3) will be performed for the CDAI-70 response, durable remission in the maintenance phase, durable CDAI-100 response in the maintenance phase, and the durable CDAI-70 response in the maintenance phase respectively. (8) Summary statistics and the 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time. Summary statistics and the 95% two-sided CI of the mean will be calculated for the CDAI scores at each visit

with stratification according to "prior TNFα antagonist use."

(9) Summary statistics and the 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time. Summary statistics and the 95% two-sided CI of the mean will be calculated for changes from baseline in the CDAI scores at each visit with stratification according to "prior TNFα antagonist use."

(10) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with change from baseline in the CDAI score at Week 60 (LOCF) as a response, the treatment group in the maintenance phase as a factor, and CDAI score at baseline as a covariate.

(11) The same analysis as (8) will be performed for each CDAI subscore at each visit.

(12) The same analysis as (9) will be performed for changes from baseline in each CDAI subscore at each visit.

2.3.3 Endpoints Related to CRP

Analysis set: Full analysis set in the maintenance phase

Analysis variables: CRP Level

CRP Level (within the reference range) [Yes, No]

Visit: Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 60, and Week 60 (LOCF)

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

(1) Summary statistics and the 95% two-sided CI of the mean will be calculated for CRP level at each visit. Summary statistics, the 95% two-sided CI of the mean, and the 10 and 90 percentiles will be calculated for changes from baseline in CRP level at each visit (Week 2 to Week 60 [LOCF]).

(2) The same analysis as (1) will be performed with stratification according to "prior TNFα antagonist use." The Wilcoxon rank sum test will be performed for changes from baseline in CRP level at Week 60 (LOCF).

(3) In the subpopulation of subjects with the baseline CRP level outside the reference range (>0.30 mg/dL), frequency distributions will be provided for subjects with CRP level within the reference range at each visit (Week 2 to Week 60 [LOCF]) 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 for the proportion of subjects whose CRP level at Week 60 (LOCF) is within the reference range.

(4) The same analysis as (3) will be performed in the

subpopulation of subjects with the baseline CRP level of >0.5 mg/dL.

(5) The same analysis as (3) will be performed in the subpopulation of subjects with the baseline CRP level of >1.0 mg/dL.

2.3.4 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 from Week 14 in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function])
- Change from Week 10 in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function])
- Change from baseline in IBDQ score (total score and each subscore [abdominal symptoms, general condition, emotion, and social function])
- IBDQ total score ≥170 [Yes, No]
- Change from baseline in IBDQ total score ≥16 [Yes, No]
- Change from Week 10 in IBDQ total score ≤-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 from Week 14 in IBDQ score)
- Weeks 14, 38, 60, and Week 60 (LOCF) (change from Week 10 in IBDQ score , and change from Week 10 in IBDQ total score ≤-16)
- Weeks 10, 14, 38, 60, and Week 60 (LOCF) (IBDQ total score ≥170, change from baseline in IBDQ score, change from baseline in IBDQ total score ≥16, change from baseline in IBDQ total score ≤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 the 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 the 95% two-sided CI of the mean will be calculated for changes from Week 14 in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at each visit.

(3) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA

model with change from Week 14 in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 60 (LOCF) as a response, the treatment group in the maintenance phase as a factor, and Week 14 value that corresponds to the score used as response as a covariate.

(4) Summary statistics and the 95% two-sided CI of the mean will be calculated for changes from Week 10 in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at each visit.

(5) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with change from Week 10 in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 60 (LOCF) as a response, the treatment group in the maintenance phase as a factor, and Week 10 value that corresponds to the score used as response as a covariate.

(6) Summary statistics and the 95% two-sided CI of the mean will be calculated for changes from baseline in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at each visit.

(7) The point estimate and 95% two-sided CI for the difference in the LS mean between treatment groups (MLN0002 group − placebo group) will be calculated based on the ANCOVA model with change from baseline in IBDQ total score and each subscore (abdominal symptoms, general condition, emotion, and social function) at Week 60 (LOCF) as a response, the treatment group in the maintenance phase as a factor, and baseline value that corresponds to the score 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 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 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 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 from Week 10 in IBDQ total score ≤-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 the 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.

2.3.5 Endpoints Related to Oral Corticosteroid Dosage

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

Analysis variables: Oral corticosteroid dosage
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 the 95% two-sided CI of the mean will be calculated for oral corticosteroid dosage at each visit.

(2) Summary statistics and the 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.

2.3.6 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

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 the 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) The log-rank test 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 Cox regression model with treatment group as independent variable.

2.4 Statistical and Analytical Issues

2.4.1 Adjustments for Covariates

Covariate-adjusted analysis will not be performed for the maintenance phase because the sample size is too small for meaningful analysis.

2.4.2 Handling of Dropouts or Missing Data

The efficacy endpoints of clinical response or clinical remission will be considered as non-response or non-remission 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.

2.4.3 Interim Analyses and Data Monitoring

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

For the open-label cohort, after the data obtained from all the subjects by the cut-off date for marketing authorization application is locked, the data up to the cut-off date for marketing authorization application will be analyzed. Continuation/termination of the study, change in clinical trial plan, and so on will not be judged based on the analysis.

2.4.4 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.

2.4.5 Multiple Comparisons/Multiplicity

Not applicable.

2.4.6 Use of an "Efficacy Subset" of Subjects

To confirm the robustness of the primary analysis results for the primary endpoint from 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."

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

Not applicable.

2.4.8 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≤ - ≤34, 35≤ - ≤Max] [Min≤ - ≤64, 65≤ - ≤Max]
	Gender	[Male, Female]
	Duration of CD (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 corticosteroids failure only]
	Prior immunomodulators and TNFα antagonist failure	[Yes, No]
	Concomitant use of enteral nutrient at baseline	[Yes, No]
	Concomitant use of 5-ASA at baseline	[Yes, No]
	Concomitant use of immunomodulators at baseline	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline	[Yes, No]
	Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline (concomitant use of oral corticosteroids only)	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline	[Yes, No]

CDAI score at baseline	[Min≤ - ≤330, 330< - ≤Max]
Clinical remission at Week 10	[Clinical remission, Non-remission]
Disease localization	[Small intestinal, Large intestinal, Small/Large intestinal]
Weight (kg) at baseline	[Min≤ - ≤59.9, 60.0≤ - ≤Max]
CRP (mg/dL) at baseline	[Min≤ - <0.3, 0.3≤ - ≤Max] [Min≤ - <0.5, 0.5≤ - ≤Max] [Min≤ - <1.0, 1.0≤ - ≤Max] [Min≤ - ≤1.6, 1.6< - ≤Max]

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

(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 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	
	Infusion reactions 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 (time)	[1, 2, 3, 4, 5, 6]

Analysis methodology: 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."

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 maintenance phase as day 1.

(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 reactions in the maintenance phase by SOC and PT

(12) Infusion reactions in the maintenance phase by study drug administration in the maintenance phase (time) 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 (time) by SOC and PT

(15) TEAEs in the maintenance phase whose incidence summarized by PT is 10% 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 the percentages of TEAEs 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 (time) by SOC and PT"
  A subject with a TEAE that occurs in more than one time of the study drug administration is counted for all the administrations (time) 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 the percentages of TEAEs 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 the first, etc., study drug 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 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	

Categories: Adjudication results based on 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

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 the

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 baseline and each post-baseline visit
(4) Shift tables showing categories of SAP Appendix 2 (1) at baseline 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 based on reference range [Below lower limit of normal range, Within normal range, Over upper limit of normal 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 baseline 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 table at baseline 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: TEAEs in the maintenance phase by SOC and PT
Infusion reactions in the maintenance phase by SOC and PT

Analysis methodology: Summaries similar to those in section 3.1.2 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 the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV% (2) Mean/standard deviation plot

4.2 Subgroup 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	
Stratum:	Prior TNFα antagonist use	[Yes, No]
	Concomitant use of 5-ASA at baseline	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	Concomitant use of immunomodulators at baseline	[Yes, No]
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 the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0. (1) Summary statistics, geometric mean, and geometric CV%	

4.3 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]
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 the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0.	

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

4.4 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 the induction and maintenance phases	[Negative, Positive]
	Persistently positive in the induction and maintenance phases	[Yes, No]
	Transiently positive in the induction and maintenance phases	[Yes, No]
	Neutralizing antibody in the 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 the geometric mean and geometric CV%, the analysis will be performed by excluding data for which serum concentration of MLN0002 is 0.	
	(1) Summary statistics, geometric mean, and geometric CV%	

4.5 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]
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]
	Serum concentrations of MLN0002 at Week 14	[0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]
	Serum concentrations of MLN0002 at Week 22	[0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]
	Serum concentrations of MLN0002 at Week 30	[0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]
	Serum concentrations of MLN0002 at Week 60	[0≤ - <Q1, Q1≤ - <Median, Median≤ - <Q3, Q3≤ - ≤Max]
Analysis methodology:	The following analysis will be performed for the above analysis variables for each stratum by treatment group in the maintenance phase. 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, and point estimates and the 95% two-sided CI for the proportion

5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS

5.1 AVA and the Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and the 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 in the induction and maintenance phases	[Yes, No]
	Transiently positive in the induction and maintenance phases	[Yes, No]
	Neutralizing antibody	[Negative, Positive]
	AVA in the induction and maintenance phases	[Negative, Positive]
	Maximum AVA titer in the induction and maintenance phases	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Neutralizing antibody in the induction and maintenance phases	[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 defined 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 the Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and the neutralizing antibody in the "full analysis set in the maintenance phase"	
Analysis variables:	Clinical remission at Week 60	[Clinical remission, Non-remission]
Stratum:	AVA in the induction and maintenance phases	[Negative, Positive]
	Persistently positive in the induction and maintenance phases	[Yes, No]
	Transiently positive in the induction and maintenance phases	[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. (1) Frequency distributions	

5.3 Subgroup Analysis of AVA and the Neutralizing Antibody

Analysis set:	Subjects who underwent proper determination of AVA and the neutralizing antibody in the "full analysis set in the maintenance phase"	
Analysis variables:	AVA in the induction and maintenance phases	[Negative, Positive]
	Persistently positive in the induction and maintenance phases	[Yes, No]
	Transiently positive in the induction and maintenance phases	[Yes, No]
	Neutralizing antibody in the induction and maintenance phases	[Negative, Positive]
Stratum:	Concomitant use of immunomodulators at baseline	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	Infusion reactions in the induction and maintenance phases	[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	25 January 2018	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 and 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 the "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 ($\times 10^4$/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 the "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 criterion, 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: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN

Label	Criteria for "elevated liver enzyme"	
	Elevated	Not elevated
		- 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 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 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 Crohn's disease

Protocol No. : MLN0002/CCT-001

Sponsor : Takeda Pharmaceutical Company Limited

Person responsible for preparing the protocol

Trial Statistician

Person responsible for pharmacokinetic/pharmacodynamic analyses

First version: 25 January 2018

TABLE OF CONTENTS

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 CDAI-70 response at Week 10: Determination of CDAI-70 response or non-CDAI-70 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	CDAI-70 Response at Week 10	Study Drug in the Maintenance Phase	Study Drug Completion Status in the Maintenance Phase	Features
Route 1	MLN0002	CDAI-70 response	MLN0002	Completed	
Route 2	MLN0002	CDAI-70 response	MLN0002	Discontinued	Reinduction to subjects with treatment failure in the maintenance phase (loss of response)
Route 3	MLN0002	CDAI-70 response	Placebo	Completed	
Route 4	MLN0002	CDAI-70 response	Placebo	Discontinued	Reinduction to subjects who achieved treatment success

Name	Study Drug in the Induction Phase	CDAI-70 Response at Week 10	Study Drug in the Maintenance Phase	Study Drug Completion Status in the Maintenance Phase	Features
					in the induction phase and were subsequently observed without any administration of the study drug but relapsed after that
Route 5	MLN0002	Non-CDAI-70 response	-	-	Reinduction to subjects with treatment failure in the induction phase (inadequate response)
Route 6	Placebo	CDAI-70 response	Placebo	Completed	
Route 7	Placebo	CDAI-70 response	Placebo	Discontinued	
Route 8	Placebo	Non-CDAI-70 response	-	-	

- Anti-vedolizumab antibody (AVA): Human anti-human antibody (HAHA) in the protocol will be described as AVA.
- Baseline: A visit at "Week 0" in the "HANDLING OF TIME WINDOW"

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 evaluable 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.

CDAI score*[1], each CDAI subscore*[2] (both based on the hematocrit [Ht] level at each study site)

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
Week 0	Study Day: 1	-28 to 1*[3]	
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	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
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	
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)*[4]	Study Day in the Open-label Cohort:	2 to	

*[1] CDAI-70 response, CDAI-100 response, and clinical remission will be determined by using both CDAI score based on the Ht level at each study site and CDAI score based on the Ht level at the central laboratory, respectively.

*[2] Each CDAI subscore used for the calculation of CDAI scores will be used.

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

*[4] 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.

Ht level*[1] (tested by the central laboratory), inflammatory marker (CRP)

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 14x	Study Day in the Open-label Cohort: 99	57 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	
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	
Week 94x (LOCF)*[3]	Study Day in the Open-label Cohort:	2 to	

*[1] The Ht level will be handled as follows:

- If the Ht level tested on the same date as the evaluation day of the CDAI score based on the Ht level at each study site is available, that Ht level will be used.
- If the Ht level tested on the same date as the evaluation day of the CDAI score based on the Ht level at each study site is not available, it will be handled according to the general rules described directly beneath the "HANDLING OF TIME WINDOW."

*[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)

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	57 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	
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*[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.

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	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
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	

Visit	Scheduled Study Day	Acceptable Window	
		Study Day in the Open-label Cohort	Follow-up Day
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	
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 survey

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

Visit	Scheduled Study Day	Acceptable Window	
		Study Day	Follow-up Day
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 (days): 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 (days): 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 (days): Date of the last dose of MLN0002 − Date of the first dose of MLN0002 + 1
- Duration on study after the first dose of MLN0002 (days): Date of last visit or contact − Date of the first dose of MLN0002 + 1
- BMI (kg/m^2) = Weight (kg) / (Height [cm]/100)^2 (round off to the first decimal place)
- Duration of CD (years): (Date of informed consent [year and month] − Date of CD diagnosis [year and month]) / 12 (round off to the first decimal place)
  - Only the year and month for the date of informed consent will be used.
  - The unit for "Date of informed consent (year and month) − Date of CD diagnosis (year and month)" will be "months."
  - If the year of CD diagnosis is unknown, the duration of CD will be handled as "Missing." If only the month of CD diagnosis is unknown, the duration of CD will be calculated by setting the month of CD diagnosis as January.
- Prior corticosteroids failure: If corticosteroid 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 corticosteroids failure is "Yes" are classified as follows:
  - Subjects for whom corticosteroid resistance is "Yes" are classified as "Resistance."
  - Among subjects for whom corticosteroid resistance is not "Yes," subjects for whom corticosteroid dependence is "Yes" are classified as "Dependence."
  - Among subjects for whom corticosteroid 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 corticosteroids 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 corticosteroid 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 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 is not "Yes," subjects for whom immunomodulatory intolerance is "Yes" are classified as "Intolerance."
- Prior TNFα antagonist failure: If inadequate response, loss of response, or intolerance to the TNFα antagonist is "Yes," prior TNFα antagonist failure will be defined as "Yes." Any response other than the above will be defined as "No."
- Number of drugs of TNFα antagonist failure: Among the drugs entered to prior treatment failure (TNFα antagonist) for CD, 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 (TNFα antagonist) for CD are classified as "None."
- Classification of prior TNFα antagonist failure: Subjects for whom prior TNFα antagonist failure is "Yes" are classified as follows:
  - Subjects for whom TNFα antagonist inadequate response is "Yes" are classified as "Inadequate response."
  - Among subjects for whom TNFα antagonist inadequate response is not "Yes," subjects for whom TNFα antagonist loss of response is "Yes" are classified as "Loss of response."
  - Among subjects for whom TNFα antagonist inadequate response is not "Yes" as well as TNFα antagonist loss of response not being "Yes," subjects for whom TNFα antagonist intolerance is "Yes" are classified as "Intolerance."
- Prior immunomodulators failure (excluding prior TNFα antagonist failure): If prior TNFα antagonist failure is "No" and prior immunomodulators failure is "Yes," prior immunomodulators failure (excluding prior TNFα antagonist failure) will be defined as "Yes." All others will be defined as "No."
- Prior corticosteroids failure only: If prior TNFα antagonist failure is "No," prior immunomodulators failure is "No," and prior corticosteroids failure is "Yes," prior corticosteroids failure only will be defined as "Yes." All others will be defined as "No."
- Prior immunomodulators and TNFα antagonist failure: If prior immunomodulators failure is "Yes" and prior TNFα antagonist failure is "Yes," prior immunomodulators and TNFα 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 ≥75%), the study drug infusion will be defined as "Completed." All others will be defined as "Incompleted."

The Ht level and CDAI score will be handled as follows:

- The CDAI score, CDAI subscore, and Ht levels used for analysis will be determined at the central laboratory unless otherwise noted.
- CDAI score: The sum of CDAI subscores of (1) to (8) defined in the table below.

(1) Number of liquid or very soft stools during the last 1 week	× 2
(2) Abdominal pain during the last 1 week (7-day total of daily abdominal pain scores on a following scale) 0=None, 1=Mild, 2=Moderate, 3=Severe	× 5
(3) Subjective general well being during the last 1 week (7-day total of daily general well-being scores on a following scale) 0=Generally well, 1=Slightly under par, 2=Poor, 3=Very poor, 4=Terrible	× 7
(4) Current number of the following extraintestinal manifestations of CD 1) Arthritis/arthralgia 2) Iritis/uveitis 3) Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis 4) Anal fissure, anal fistula, or perianal abscess 5) Other fistula 6) Fever over 37.8°C during the last 1 week	× 20
(5) Use of antidiarrheal drugs (e.g., lopemin) or opiates for diarrhea 0=No, 1=Yes	× 30
(6) Abdominal mass 0=None, 2=Questionable, 5=Definite	× 10
(7) Hematocrit (%)[Note 1)] Males: subtract value from 47, Females: subtract value from 42	× 6
(8) Body weight : Standard weight (body-weight ratio)[Note 2)] [1 − (Body weight / Standard weight)] × 100	× 1

Note 1) If hematocrit subtotal <0, enter 0.

Note 2) If body weight subtotal <-10, enter -10.

- The CDAI score will be calculated using subscores on the same day of evaluation. For subscore (7), however, the CDAI score will be calculated using the Ht level obtained within the same visit window if the Ht level on the same day of evaluation is not available.
- If any CDAI subscore is missing, the CDAI score will be handled as missing.
- CDAI-70 response: Subjects will be classified as "CDAI-70 response" if "a ≥70-point decrease in CDAI score from baseline" is achieved. All others will be classified as "Non-CDAI-70 response." However, if any CDAI score change 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 the "HANDLING OF TIME WINDOW," subjects will be classified as "Non-CDAI-70 response."
- CDAI-100 response: Subjects will be classified as "CDAI-100 response" if "a ≥100-point decrease in CDAI score from baseline" is achieved. All others will be classified as "Non-CDAI-100 response." However, if any CDAI score change 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 the "HANDLING OF TIME WINDOW," subjects will be classified as "Non-CDAI-100 response."
- Clinical remission: Subjects will be classified as "Clinical remission" if a "CDAI score of ≤150" is achieved. All others will be classified as "Non-remission." However, if any of the CDAI scores 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 the "HANDLING OF TIME WINDOW," subjects will be classified as "Non-remission."

Prior TNFα antagonist use, concomitant use of immunomodulators at baseline, and concomitant use of oral corticosteroids at baseline will be defined as follows:

- Prior TNFα 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 baseline: Subjects who received any concomitant medication (for treatment of CD) which is classified as "immunomodulator" in the concomitant medication (for treatment of CD) 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 CD) 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 baseline: Subjects who received any concomitant medication (for treatment of CD) which is classified as "corticosteroid" and whose route of administration is "oral" in the concomitant medication (for treatment of CD) 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 CD) which was started after the first dose of the study drug in the induction phase is not subject to this handling.

Concurrent extraintestinal manifestations (based on CDAI subscore [4]), concurrent extraintestinal manifestations (based on case report form [CRF] concurrent medical condition section), surgical history for CD, medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent, and concurrent medical condition related to fistula will be defined as follows:

- Concurrent extraintestinal manifestations (based on CDAI subscore [4]): Subjects whose CDAI subscore [4] at baseline is greater than 0 will be classified as "Yes." All others will be classified as "No."
- Concurrent extraintestinal manifestations (based on CRF concurrent medical condition section): Subjects recorded to have concurrent extraintestinal manifestations of CD in the CRF concurrent medical condition section will be classified as "Yes." All others will be classified as "No."
- Surgical history for CD: Subjects coded with at least one PT in the following table for medical history will be classified as "Yes." All others will be classified as "No."

Preferred Term
Anal skin tag excision
Colectomy
Crohn's disease
Enterocutaneous fistula
Ileal operation
Ileectomy
Ileocolectomy
Ileocolostomy
Ileostomy
Ileostomy closure
Intestinal resection
Proctectomy
Sigmoidectomy
Small intestinal resection
Small intestine operation
Stricturoplasty
Urinary cystectomy

- Medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent: Subjects coded with at least one PT in the following table for medical history or concurrent medical condition will be classified as “Yes.” All others will be classified as “No.”

Medical history

Preferred Term
Anal fistula
Fistula of small intestine

Concurrent medical condition

Preferred Term
Anal fistula
Enterocutaneous fistula
Female genital tract fistula

- Concurrent medical condition related to fistula: Subjects coded with at least one PT in the following table for concurrent medical condition will be classified as “Yes.” All others will be classified as “No.”

Preferred Term
Anal fistula
Enterocutaneous fistula
Female genital tract fistula

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. The neutralizing antibody will be handled as missing if it does not correspond to any

of the above.

After determining the negative or positive status of the neutralizing antibody at each visit with the above-mentioned logic, the following determination will be made:

- 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.
- Persistently positive in the induction phase, maintenance phase, and open-label cohort
  - "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" will be classified as persistently positive.
- Transiently positive in the induction phase, maintenance phase, and open-label cohort
  - 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 were 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.
- 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.

- Start date of concomitant medication/therapy in the open-label cohort that falls under the category of rescue treatment: The earliest date among the following dates in the open-label cohort.
  - Date of the first dose of concomitant medication (for treatment of CD) that falls under the category of rescue treatment
  - Date of initiation of concomitant therapy that falls under the category of rescue treatment

- Start date of concomitant medication/therapy in the open-label cohort: The earliest date among the following dates in the open-label cohort.
  - Date of the first dose of concomitant medication (for treatment of CD)
  - Date of initiation of concomitant therapy

Lymphocytes and neutrophils will be calculated with the following formula:

- Lymphocytes = WBC × lymphocytes (%)
- Neutrophils = WBC × 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 the 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 the percentages of the reasons for not being completed, the number of subjects who did not complete 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 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]
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]

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

Frequency distribution of subjects with protocol deviations in the open-label cohort will be provided for each deviation category above. 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 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:	The following analyses of (1) to (3) will be performed for the above analysis variables.	
	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 open-label cohort in each analysis set	
	(2) Frequency distributions concerning the handling of subject data in the open-label cohort 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 open-label cohort	
Analysis variables:	Age (years)	[Min≤ - ≤34, 35≤ - ≤Max]
		[Min≤ - ≤64, 65≤ - ≤Max]
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg) at baseline	[Min≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
	BMI (kg/m^2) at baseline	[Min≤ - ≤18.4, 18.5≤ - ≤24.9, 25.0≤ - ≤Max]
	Smoking classification	[Never smoked, Current smoker, Ex-smoker]
	Duration of CD (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 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 corticosteroids failure only]
Prior immunomodulators and TNFα antagonist failure	[Yes, No]
Prior TNFα antagonist use	[Yes, No]
Infliximab	[Yes, No]
Adalimumab	[Yes, No]
Golimumab	[Yes, No]
Concomitant use of enteral nutrient at baseline	[Yes, No]
Concomitant use of 5-ASA at baseline	[Yes, No]
Concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids at baseline	[Yes, No]
No concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline	[Yes, No]
Concomitant use of oral corticosteroids and No concomitant use of immunomodulators at baseline (concomitant use of oral corticosteroids only)	[Yes, No]
No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
Concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline	[Yes, No]
CDAI score at baseline	[Min≤ - ≤220, 220< - ≤330, 330< - ≤450, 450< - ≤Max]
CDAI subscore (1): Number of liquid or very soft stools during the last 1 week at baseline	

CDAI subscore (2): Abdominal pain during the last 1 week at baseline	
CDAI subscore (3): Subjective general well being during the last 1 week at baseline	
CDAI subscore (4): Current number of extraintestinal manifestations of CD (e.g., arthritis/arthralgia) at baseline	[0, 1, 2, 3, 4, 5, 6]
CDAI subscore (5): Use of antidiarrheal drugs (e.g., lopemin) or opiates for diarrhea at baseline	[No, Yes]
CDAI subscore (6): Abdominal mass at baseline	[None, Questionable, Definite]
CDAI subscore (7): Hematocrit level at baseline	
CDAI subscore (8): Body weight : Standard weight (body-weight ratio) at baseline	
Disease localization	[Small intestinal, Large intestinal, Small/Large intestinal]
Concurrent extraintestinal manifestations (based on CDAI subscore [4])	[Yes, No]
Concurrent extraintestinal manifestations (based on CRF concurrent medical condition section)	[Yes, No]
CRP (mg/dL) at baseline	[Min≤ - ≤0.3, 0.3< - ≤0.5, 0.5< - ≤1.0, 1.0< - ≤1.6, 1.6< - ≤Max]
Surgical history for CD	[Yes, No]
Medical history of fistula or concurrent medical condition related to fistula within 1 year before signing of informed consent	[Yes, No]
Concurrent medical condition related to fistula	[Yes, No]
Number of MLN0002 infusions 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 CD)

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

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 CD) (by SOC and PT)

(3) Frequency distributions for concurrent medical conditions (other than concurrent extraintestinal manifestations of CD) (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, Concomitant Therapies

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

Analysis variables: Medication history

Concomitant medications (for treatment of CD) in the open-label cohort

Classification of concomitant medications (for treatment of CD) in the open-label cohort [5-ASA, Corticosteroids, Immunomodulators, Enteral nutrients, Other]

Concomitant medications (for treatment of CD) in the open-label cohort that fall under the category of rescue treatments

	Classification of concomitant medications (for treatment of CD) in the open-label cohort that fall under the category of rescue treatments	[5-ASA, Corticosteroids, Immunomodulators, Enteral nutrients, Other]
	Concomitant medications (for other than treatment of CD) in the open-label cohort	
	Concomitant therapies in the open-label cohort	[Yes, No]
	Concomitant therapies in the open-label cohort that fall under the category of rescue treatments	[Yes, No]

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

Medication history, concomitant medications (for treatment of CD) in the open-label cohort, concomitant medications (for treatment of CD) in the open-label cohort that fall under the category of rescue treatments, and concomitant medications (for other than treatment of CD) 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 CD) 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 CD) 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 CD) 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 CD) 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 CD) 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 CD) 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 the 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 infusions 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 incompleted 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 incompleted 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 incompleted infusions will be counted as frequency for “Incompleted.” When calculating the percentage, the sum of the number of completed infusions and the number of incompleted 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 CDAI Scores

Analysis set:	Full analysis set in the open-label cohort	
Analysis variables:	Clinical remission	[Clinical remission, Non-remission]
	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	CDAI score change over time	
	Each CDAI subscore change over time	
Stratum:	Route to the open-label cohort	[Route 1, Route 2, Route 3, Route 4, Route 5, Route 6, Route 7, Route 8]
Visit:	Weeks 0, 0x, 2x, 6x, 14x, 22x, 30x, 38x, 46x, 54x, 62x, 70x, 78x, 86x, 94x, and Week 94x (LOCF) (Clinical remission, CDAI-100 response, CDAI-70 response, CDAI score change over time, each CDAI subscore change over time)	
Analysis methodology:	The following analysis will be performed for the above analysis variables.	

(1) Frequency distributions will be provided for clinical remission at each visit along with the point estimate and 95% two-sided CI for the proportion.

(2) Frequency distributions will be provided for clinical remission at each visit with stratification according to “prior TNFα antagonist use” along with the point estimate and 95% two-sided CI for the proportion.

(3) The same analysis as (1) will be performed for the CDAI-100 response at each visit.

(4) The same analysis as (2) will be performed for CDAI-100 response at each visit with stratification according to “prior TNFα antagonist use.”

(5) The same analysis as (1) will be performed for the CDAI-70 response at each visit.

(6) The same analysis as (2) will be performed for CDAI-70 response at each visit with stratification according to “prior TNFα antagonist use.”

(7) Summary statistics and the 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time.

(8) Summary statistics and the 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time.

(9) The same analysis as (7) will be performed for each CDAI subscore at each visit.
(10) The same analysis as (8) will be performed for changes from baseline in each CDAI subscore at each visit.
(11) The same analysis as (1) will be performed for clinical remission at each visit by route to the open-label cohort.
(12) The same analysis as (2) will be performed for clinical remission at each visit by route to the open-label cohort.
(13) The same analysis as (1) will be performed for CDAI-100 response at each visit by route to the open-label cohort.
(14) The same analysis as (2) will be performed for CDAI-100 response at each visit by route to the open-label cohort.
(15) The same analysis as (1) will be performed for CDAI-70 response at each visit by route to the open-label cohort.
(16) The same analysis as (2) will be performed for CDAI-70 response at each visit by route to the open-label cohort.
(17) The same analysis as (7) will be performed for CDAI score at each visit by route to the open-label cohort.
(18) The same analysis as (8) will be performed for changes from baseline in the CDAI scores at each visit by route to the open-label cohort.

2.1.2 Endpoints Related to CDAI Scores Based on the Hematocrit Level at Each Study Site

Analysis set:	Full analysis set in the open-label cohort	
Analysis variables:	Clinical remission	[Clinical remission, Non-remission]
	CDAI-100 response	[CDAI-100 response, Non-CDAI-100 response]
	CDAI-70 response	[CDAI-70 response, Non-CDAI-70 response]
	CDAI score change over time	
	Each CDAI subscore change over time	
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 Week 94x (LOCF) (Clinical remission, CDAI-100 response, CDAI score change over time, each CDAI subscore change over time)	
Analysis methodology:	Each analysis variable will be determined using the CDAI score based on the Ht level at each study site and CDAI subscores.	

The following analysis will be performed for the above analysis variables.

(1) Frequency distributions will be provided for clinical remission at each visit along with the point estimate and 95% two-sided CI for the proportion.
(2) Frequency distributions will be provided for clinical remission at each visit with stratification according to “prior TNFα

antagonist use" along with the point estimate and 95% two-sided CI for the proportion.

(3) The same analysis as (1) will be performed for the CDAI-100 response at each visit.
(4) The same analysis as (2) will be performed for CDAI-100 response at each visit with stratification according to "prior TNFα antagonist use."
(5) The same analysis as (1) will be performed for the CDAI-70 response at each visit.
(6) The same analysis as (2) will be performed for CDAI-70 response at each visit with stratification according to "prior TNFα antagonist use."
(7) Summary statistics and the 95% two-sided CI of the mean will be provided for the CDAI scores at each visit along with the plot over time.
(8) Summary statistics and the 95% two-sided CI of the mean will be provided for changes from baseline in the CDAI scores at each visit along with the plot over time.
(9) The same analysis as (5) will be performed for each CDAI subscore at each visit.
(10) The same analysis as (6) will be performed for changes from baseline in each CDAI subscore at each visit.

2.1.3 Endpoints Related to CRP

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

Analysis variables: CRP Level
CRP Level (within the reference range) [Yes, No]

Visit: Weeks 0, 0x, 2x, 6x, 14x, 22x, 30x, 38x, 46x, 54x, 62x, 70x, 78x, 86x, 94x, and Week 94x (LOCF)

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

(1) Summary statistics and the 95% two-sided CI of the mean will be calculated for CRP level at each visit (baseline to Week 60). Summary statistics, the 95% two-sided CI of the mean, and the 10 and 90 percentiles will be calculated for changes from baseline in CRP level at each visit (Week 2 to Week 60).
(2) The same analysis as (1) will be performed with stratification according to "prior TNFα antagonist use."
(3) In the subpopulation of subjects with the baseline CRP level outside the reference range (>0.30 mg/dL), frequency distributions will be provided for subjects with CRP level within the reference range at each visit (Week 0x to Week 94x [LOCF]) along with the point estimate and 95% two-sided CI for the proportion.
(4) The same analysis as (3) will be performed in the subpopulation of subjects with the baseline CRP level of >0.5 mg/dL.

(5) The same analysis as (3) will be performed in the subpopulation of subjects with the baseline CRP level of >1.0 mg/dL.

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 or clinical remission will be considered as non-response or non-remission 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.

2.2.3 Interim Analyses and Data Monitoring

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

For the open-label cohort, after the data obtained from all the subjects by the cut-off date for marketing authorization application is locked, the data up to the cut-off date for marketing authorization application will be analyzed. Continuation/termination of the study, 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 in the open-label cohort (time)	[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]

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.

(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 reactions in the open-label cohort by SOC and PT

(12) Infusion reactions in the open-label cohort by study drug administration in the open-label cohort (time) 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 (time) 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 TEAEs 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 TEAEs 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 the percentages of TEAEs 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 TEAEs 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 (time) by SOC and PT"
  A subject with a TEAE that occurs in more than one time of the study drug administration is counted for all the administrations (time) 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 the percentages of TEAEs 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 the first, etc., study drug administration in the open-label cohort"

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 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	

Categories: Adjudication results based on 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, 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)

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 the 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 baseline and each post-baseline visit
(4) Shift tables showing categories of SAP Appendix 2 (1) at baseline 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 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 baseline 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 table at baseline 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 variables:	TEAEs in the open-label cohort by SOC and PT Infusion reactions in the open-label cohort by SOC and PT
Analysis methodology:	Summaries similar to those in section 3.1.2 will be provided for the above analysis variables. SOC and PT will be displayed in Japanese.

5 ANALYSIS OF IMMUNOGENICITY ENDPOINTS

5.1 AVA and the 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 in the induction phase, maintenance phase, and open-label cohort	[Yes, No]
	Transiently positive in the induction phase, maintenance phase, and open-label cohort	[Yes, No]
	Neutralizing antibody	[Negative, Positive]
	AVA in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
	Maximum AVA titer in the induction phase, maintenance phase, and open-label cohort	[1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250]
	Neutralizing antibody in the induction phase, maintenance phase, and open-label cohort	[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 defined according to the observed AVA titer.	
	(1) Frequency distributions	

5.2 Efficacy by AVA and the 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 remission at Week 94x (LOCF)	[Clinical remission, Non-remission]
Stratum:	AVA in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
	Persistently positive in the induction phase, maintenance phase, and open-label cohort	[Yes, No]
	Transiently positive in the induction phase, maintenance phase, and open-label cohort	[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 Subgroup Analysis of AVA and the 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 in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
	Persistently positive in the induction phase, maintenance phase, and open-label cohort	[Yes, No]
	Transiently positive in the induction phase, maintenance phase, and open-label cohort	[Yes, No]
	Neutralizing antibody in the induction phase, maintenance phase, and open-label cohort	[Negative, Positive]
Stratum:	Concomitant use of immunomodulators at baseline	[Yes, No]
	No concomitant use of oral corticosteroids and Concomitant use of immunomodulators at baseline (concomitant use of immunomodulators only)	[Yes, No]
	Concomitant use of oral corticosteroids at baseline	[Yes, No]
	Infusion reactions in the induction phase, maintenance phase, and open-label cohort	[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 infusions (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 the 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	
	Infusion reactions 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 (time) [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 reactions after the first dose of MLN0002 by SOC and PT

(12) Infusion reactions after the first dose of MLN0002 by MLN0002 administration (time) 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 (time) 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 the percentages of TEAEs 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 (time) 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 (time) 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 the percentages of TEAEs 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 TEAEs after the first dose of MLN0002 is at the time of the 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: TEAEs after the first dose of MLN0002 by SOC and PT

Infusion reactions after the first dose of MLN0002 by SOC and PT

Analysis methodology: Summaries similar to those in section 6.2.2 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 the 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, Not available]

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
- "Not available": 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	25 January 2018	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 and 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 the "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 ($\times 10^4$/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 the "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 criterion, 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: - 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	Either ALT is non-missing and less than

Label	Criteria for "elevated liver enzyme"	
	Elevated	Not elevated
	times the ULN	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 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.