STATISTICAL ANALYSIS PLAN

Protocol No. 4083-002

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Multiple Ascending Dose Study (Induction Therapy and Long-term Extension Therapy) of an Anti-OX40 Monoclonal Antibody (KHK4083) in Subjects with Moderately Active Ulcerative Colitis

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Document Information	
Protocol Number:	4083-002
Version:	Final 2.0
Document Date:	06 Oct 2017
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APPROVAL PAGE

The Statistical Analysis Plan has been completed and reviewed and the contents are approved for use for the analysis.

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Contents

Abbreviations

AEs	adverse events
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CI	confidence interval
CRF	case report form
ECGs	electrocardiograms
eCRF	electronic case report form
FAS	full analysis set
FSH	follicle-stimulating hormone
HRQL	health-related quality of life
IBDQs	inflammatory bowel disease questionnaires
ICF	informed consent form
IRT	interactive response technology
IV	intravenous
KKD	Kyowa Kirin Pharmaceutical Development, Inc.
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
mMES	modified mayo endoscopy subscore
MMRM	mixed model for repeated measures
OLE	open-label extension
PD	pharmacodynamic
PGX	pharmacogenomics
PK	pharmacokinetics
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SAS®	statistical analysis software®
SBP	systolic blood pressure
SOC	system organ class
TEAE	treatment-emergent adverse event
TNFR	tumor necrosis factor receptor
UC	ulcerative colitis
UCEIS	ulcerative colitis endoscopic index of severity
US	United States
wr-CRP	wide-range C-reactive protein

Revision History

Document Version	Changes Made	Document Date
Version Draft 1.0	First draft based on Protocol draft 4083-002, dated 07 July 2015 and Final CRF, dated 23 Nov 2015.	31 Mar 2016
Version Draft 2.0	Second draft based on Protocol 4083-002 Amendment 1, dated 15 Oct 2015 and Final CRF, dated 23 Nov 2015.	08 Apr 2016
Version Draft 3.0	Third draft based on Sponsor revision of draft version 2.0	12 May 2016
Version Draft 4.0	Third draft based on Sponsor revision of draft version 3.0	25 Oct 2016
Version 1		09 Dec 2016
Version 2	Amended for denominator changes, TLF list changes, and unblinding at Week 12.	06 Oct 2017

1. Introduction

Ulcerative colitis (UC) is considered as one of the common gastrointestinal autoimmune diseases, and is referred to as immune-mediated inflammatory disease. KHK4083 is a fully human, non-fucosylated IgG1 monoclonal antibody (mAb) specific for the costimulatory molecule OX40, a tumor necrosis factor receptor (TNFR) family member. KHK4083 binds with high affinity and specificity to an extracellular domain epitope of OX40, which plays a key role in maintaining late T-cell proliferation and survival by suppressing apoptosis, and in inducing T-cell memory formation.

This study will determine the safety and tolerability of administration of multiple ascending doses of KHK4083, and determine if the recommended dose of KHK4083 improves the mucosa in subjects with moderately active UC.

This statistical analysis plan (SAP) describes the statistical analysis and summary to be performed for the study described in Protocol 4083-002 Amendment 2, dated 04 Oct 2016 and titled:

"*A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Multiple Ascending Dose Study (Induction Therapy and Long-term Extension Therapy) of an Anti-OX40 Monoclonal Antibody (KHK4083) in Subjects with Moderately Active Ulcerative Colitis*"

The purpose of this SAP is to outline the planned analyses of clinical efficacy and safety data to be performed to support the completion of the Clinical Study Report (CSR) for Protocol 4083-002. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. The analyses of pharmacokinetic (PK) and immunogenicity data are not detailed in this SAP, and will come under separate cover. Also, exploratory analyses not identified in this SAP may be performed to support the clinical development program.

The reader of this SAP is encouraged to also read the clinical protocol and annotated case report forms (eCRFs) for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

2. Study Objectives

The primary, secondary, and exploratory objectives of the study are as follows:

2.1 Primary objectives

- **Induction Therapy - Part A:** To determine the safety and tolerability of administration of multiple ascending doses of KHK4083 and to select the highest dose tolerated by subjects with moderately active UC to recommend for use in Part B;

- **Induction Therapy - Part B:** To determine if the recommended dose of KHK4083 identified in Part A improves the mucosa in subjects with moderately active UC at Week 12 as measured by the modified Mayo endoscopy subscore (mMES).

2.2 Secondary objectives

- To determine if KHK4083 at dose levels different than the recommended dose improve the mucosa based on the mMES;
- To determine if any dose level of KHK4083 administered as Induction Therapy will meet the following objectives at Week 12:

  - Improve the mucosa based on the modified Baron endoscopic score;
  - Improve the mucosa based on the Ulcerative Colitis Endoscopic Index of Severity (UCEIS);
  - Induce mucosal healing based on the mMES;
  - Improve clinical signs and symptoms based on total Mayo Clinic score;
  - Improve clinical signs and symptoms based on partial Mayo Clinic scores (Week 2 through Week 12, excludes endoscopy subscores);
  - Induce a clinical response based on a reduction in the total Mayo Clinic score (i.e., reduction of at least 3 points and a decrease of at least 30% from Baseline [Week 0] to Week 12) and rectal bleeding subscale (i.e., reduction of at least 1 point from Baseline [Week 0] to Week 12) (or a defined absolute rectal bleeding score of 0 or 1 at Week 12);
  - Induce clinical remission based on a total Mayo Clinic score (i.e., score of ≤ 2) and subscores (i.e., no subscores > 1).

- To characterize the PK of KHK4083 in subjects with moderately active UC following multiple dose administration;
- To evaluate the development of antibodies against KHK4083 (immunogenicity).

2.3 Exploratory objectives

- To determine if multiple doses of KHK4083 administered during Open-label Extension (OLE) or Long-term Extension (LTE) Therapy will meet the following objectives at Week 52 (or as noted) when compared with Baseline (Week 0) scores (or subscores) or assessments:

  - Improve clinical signs and symptoms based on total Mayo Clinic score;
  - Improve clinical signs and symptoms based on partial Mayo Clinic scores (excludes endoscopy subscores) at Week 16 through Week 52, and the OLE/LTE Therapy Follow-up Period (Week 56 through Week 64);
  - Induce a clinical response based on a reduction in the total Mayo Clinic score and rectal bleeding subscale (or a defined absolute rectal bleeding score);
  - Induce clinical remission based on a total Mayo Clinic score and subscores;
  - Induce durable clinical responses and durable clinical remissions (present at both Weeks 12 and 52), and glucocorticoid-free clinical remission;
  - Induce mucosal healing based on the mMES;

- Improve the mucosa based on the mMES, UCEIS, and/or modified Baron endoscopic score;
- Induce a remission (Week 12; Week 52) based on modified Mayo endoscopy, stool frequency, and rectal bleeding subscores (defined as an mMES of 0 or 1, stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0).

- To evaluate the activity of KHK4083 on health-related quality of life (HRQL), which will be based on the subject's completed Inflammatory Bowel Disease Questionnaires (IBDQs) in comparison to Baseline assessments;
- To measure changes from Baseline in corticosteroid (glucocorticoid) dosages;
- To determine the percentage of subjects who are glucocorticoid-free from Week 16 through Week 52, and through the OLE/LTE Therapy Follow-up Period (Week 56 through Week 64);
- To evaluate the pharmacodynamic (PD) profile of KHK4083;
- To explore the PK-PD relationships.

3. Study Design

3.1 General design and plan

To show the changes in the study design among protocols, the Study design is described in Table 1, and the Study design diagrams are displayed in Figure 1 and Figure 2. However, as the subject enrollment started after Protocol Amendment 1, Protocol version 1 is not included.

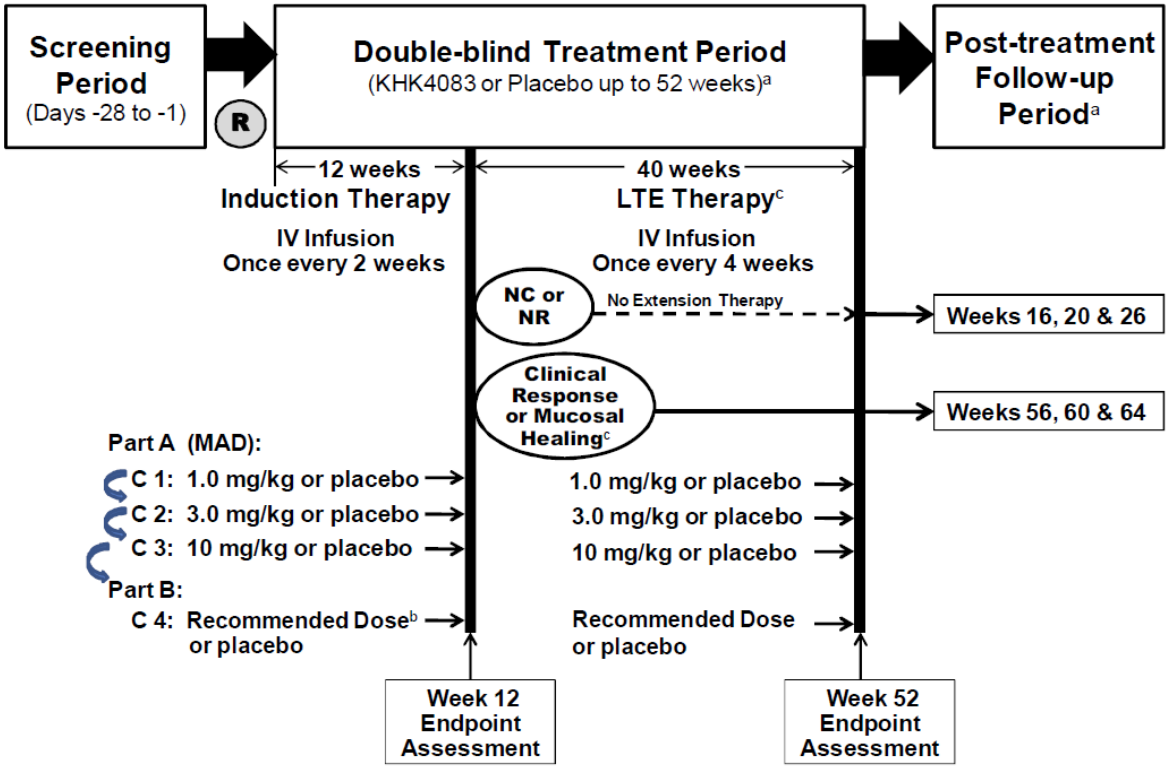
Table 1 Study Design

	Protocol Amendment 1	Protocol Amendment 2
Overall Study Design and Plan	This Phase 2, double-blind clinical study of multiple ascending doses of KHK4083 (or placebo) with an LTE Therapy phase will be conducted in approximately 60 randomized adult subjects with moderately active UC who have a documented unsuccessful previous treatment. The study will include a 4-week Screening Period, followed by a total of up to 64 weeks (treatment and follow-up) on study from the time of randomization to study completion. The Treatment Period includes double-blind Induction Therapy (12 weeks) and double-blind LTE Therapy (40 weeks) for eligible subjects at Week 12. Post-treatment assessments will continue for 16 weeks after the last infusion associated with the subject's treatment period. The on-site follow-up visits will be at Weeks 16, 20, and 26 for subjects who only receive Induction Therapy or at Weeks 56, 60, and 64 for subjects who receive both Induction and LTE Therapies. The date of the subject's last post-treatment study visit will be considered the End of Study date.	This Phase 2, double-blind clinical study of multiple ascending doses of KHK4083 (or placebo) with an OLE Therapy phase will be conducted in approximately 60 randomized adult subjects with moderately active UC who have a documented unsuccessful previous treatment. The study will include a 4-week Screening Period, followed by a total of up to 64 weeks (treatment and follow-up) on study from the time of randomization to study completion. The Treatment Period includes double-blind Induction Therapy (12 weeks) and OLE Therapy (40 weeks) for eligible subjects at Week 12. Subjects already enrolled in the double-blind, LTE under preceding versions of the protocol who worsen may be eligible to transition to the OLE up to Week 28. Post-treatment assessments will continue for 16 weeks after the last infusion associated with the subject's treatment period. The on-site follow-up visits will be at Weeks 16, 20, and 26 for subjects who only receive Induction Therapy or at Weeks 56, 60, and 64 for subjects who receive both Induction and OLE/LTE Therapies. The date of the subject's last post-treatment study visit will be considered the End-of-Study date.
Induction Therapy: Week 0 to Week 12 (Last Dose at Week 10)	Double-blind Induction Therapy is separated into Part A for administration of multiple ascending IV doses of KHK4083 (or placebo) to subjects in Cohorts 1 - 3 and Part B for administration of the recommended IV dose (one of three dose levels identified in Part A) of KHK4083 (or placebo) to subjects in Cohort 4. Subjects in Part A are prohibited from participating in Part B.	Double-blind Induction Therapy is separated into Part A for administration of multiple ascending IV doses of KHK4083 (or placebo) to subjects in Cohorts 1 - 3 and Part B for administration of the recommended IV dose (one of three dose levels identified in Part A) of KHK4083 (or placebo) to subjects in Cohort 4. Subjects in Part A are prohibited from participating in Part B.

	Protocol Amendment 1	Protocol Amendment 2
Long-term Extension Therapy: Week 12 (First Dose) to Week 52	Subjects who complete double-blind Induction Therapy (i.e., at least five of six treatments) and have a clinical response or mucosal healing are eligible to continue in double-blind LTE Therapy All subjects who qualify will be given two options: 1) To receive no further treatment and proceed directly to the Induction Therapy Follow-up Period (Week 16 through Week 26); or 2) To continue in double-blind LTE Therapy and receive 10 additional treatments of KHK4083 (at the same dose administered to that subject during Induction Therapy) or placebo as maintenance therapy. Each subject will receive one IV infusion every 4 weeks from Week 12 to Week 48 followed by an End-of-LTE Therapy visit at Week 52, and then proceed to the LTE Therapy Follow-up Period (Week 56 through Week 64). Refer to Section 8.1.4.2 for additional dosing details in LTE Therapy. All other subjects, including those who do not complete double-blind Induction Therapy (non-completers), do not meet the criteria for a clinical response, or do not have mucosal healing at Week 12 will receive no further treatment, and thus enter the Induction Therapy Follow-up Period.	The LTE is only active for subjects who entered it prior to approval of Amendment 2. Subjects who sign an ICF under Amendment 2 are eligible for the OLE. Subjects who completed double-blind Induction Therapy (i.e., at least five of six treatments) and had a clinical response or mucosal healing were eligible to continue in double-blind LTE Therapy. All subjects who qualified were to have been given two options: 1) To receive no further treatment and proceed directly to the Induction Therapy Follow-up Period (Week 16 through Week 26); or 2) To continue in double-blind LTE Therapy and receive 10 additional treatments of KHK4083 (at the same dose administered to that subject during Induction Therapy) or placebo as maintenance therapy. Each subject will receive one IV infusion every 4 weeks from Week 12 to Week 48 followed by an End-of-LTE Therapy visit at Week 52, and then proceed to the LTE Therapy Follow-up Period (Week 56 through Week 64). Note: Subjects who already started treatment in the double-blind LTE Therapy will continue to receive KHK4083 or placebo during LTE Therapy. If their UC worsens or flares up to Week 28, they may transition to OLE therapy. Subjects who did not qualify were to have received no further treatment and entered the Induction Therapy Follow-up Period.

	Protocol Amendment 1	Protocol Amendment 2
Open-label Extension Therapy: Week 12 (First Dose) to Week 52		Subjects who complete double-blind Induction Therapy (i.e., at least five of six treatments) are eligible to enter OLE Therapy (refer to Section 7.4 for specific eligibility criteria). All subjects who qualify will be given two options: 1) To receive no further treatment and proceed directly to the Induction Therapy Follow-up Period (Week 16 through Week 26); or 2) To receive 10 treatments of open-label KHK4083 (at the same dose administered to that subject during Induction Therapy) as maintenance therapy. Each subject will receive one IV infusion every 4 weeks from Week 12 to Week 48 followed by an End-of-OLE Therapy visit at Week 52, and then proceed to the OLE Therapy Follow-up Period (Week 56 through Week 64). Subjects participating in the double-blind LTE who experience a clinical worsening or a flare of disease up to Week 28, as defined by the Investigator, may transition to the OLE. Subjects will maintain the same visit schedule, e.g., a subject who completed a Week 20 visit in the LTE and transitions to the OLE at Week 24 will have an OLE Week 24 visit. However, for the first two open-label doses in the OLE, additional safety monitoring will include ECGs and post-infusion monitoring as performed for the OLE Week 12 and Week 16 visits, respectively.

Figure 1 Study Design Diagram in Protocol Amendment 1



NC or NR **Non-completer (NC) – Subject did not complete Induction Therapy; or Non-responder (NR) – Subject did not meet the criteria of a clinical response at Week 12.**

R **Randomization to double-blind Induction Therapy.**

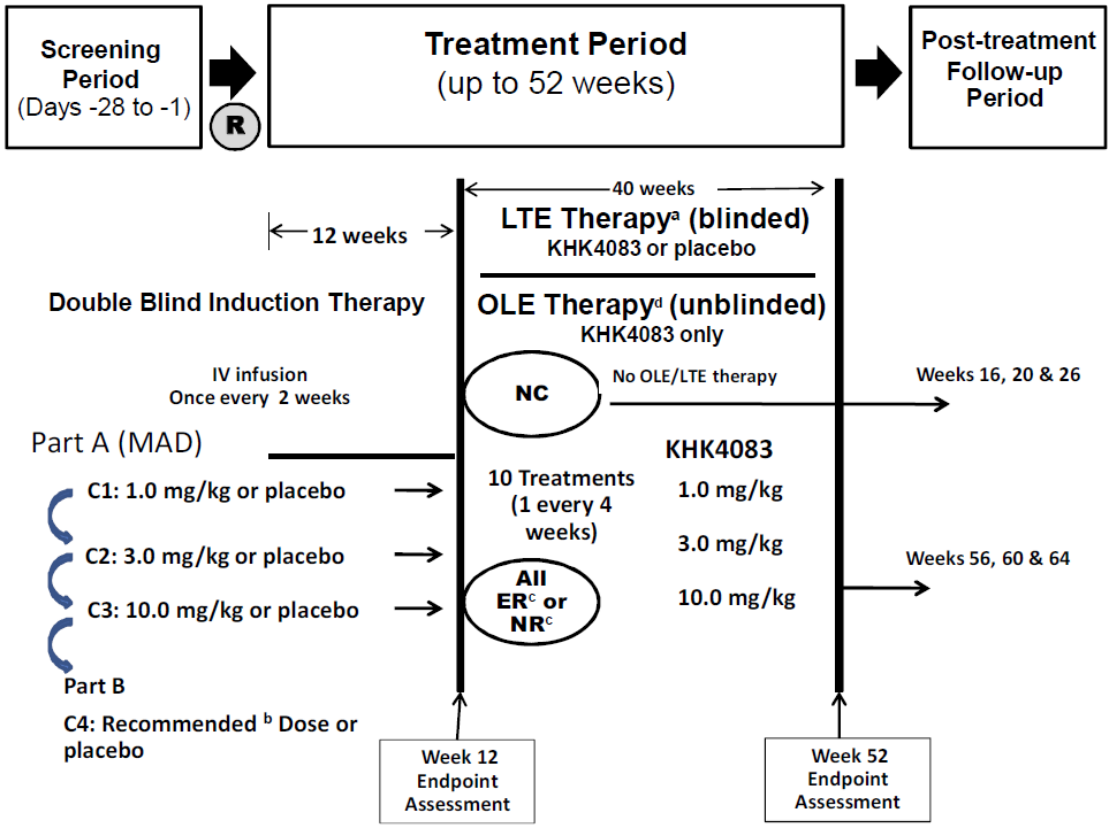
a: Subjects will be in the study for a total of up to 64 weeks from the time of randomization to study completion. The double-blind Treatment Period includes Induction Therapy (12 weeks) and Long-term Extension (LTE) Therapy (40 weeks). A post-treatment Follow-up Period will be conducted either at Weeks 16, 20, and 26 for subjects who only receive Induction Therapy or at Weeks 56, 60, and 64 for subjects who receive both Induction and LTE Therapies.

b: Cohort 4 will receive the recommended dose (1.0, 3.0 or 10 mg/kg) determined from safety assessments of Cohorts 1 - 3 in Part A.

c: Subjects who complete Induction Therapy, have evaluable total Mayo Clinic scores, and have met the criteria for a clinical response or mucosal healing will have the option to continue in LTE Therapy. Subjects who qualify will receive 10 additional treatments (one IV infusion every 4 weeks) of KHK4083 (at the same dose administered to that subject during Induction Therapy) or placebo. *(Note: Subjects administered placebo during Induction Therapy will receive placebo during LTE Therapy).*

C=cohort; LTE=long-term extension; MAD=multiple ascending dose.

Figure 2 Study Design Diagram in Protocol Amendment 2



Non-completer (NC) - Subject did not complete Induction Therapy

a: **For those subjects who enrolled under Amendment #1**- Subjects will be in the study for a total of up to 64 weeks. The double blind treatment period includes Induction Therapy (12 weeks) and LTE therapy (40 weeks). A post treatment follow-up period will be conducted at either Weeks 16, 20 and 26 for subjects who only receive Induction Therapy or at weeks 56, 60 and 64 for subjects who receive both induction and LTE Therapies

b: Cohort 4 will receive the recommended dose (1.0, 3.0, or 10 mg/kg) determined from safety assessments of Cohorts 1 - 3 in Part A.

c: Endoscopic Responders (ER) include subjects who met the criteria for clinical response at Week 12 and non-responders (NR) includes subjects who did not meet the criteria of a clinical response at Week 12.

d: **For those subjects who enroll under Amendment #2-**All subjects who complete the induction period, i.e., (received at least of 5 of the 6 doses of double-blind therapy and have Week 12 sigmoidoscopy results from the central reader) and are eligible to continue on in the study have the option to enter the OLE therapy part of the trial and receive 10 additional treatments of KHK4083 once every 4 weeks from week 12 through week 48 at the same dose used in the cohort that they were enrolled in.

C=cohort; IV=intravenous; LTE=long-term extension; OLE=Open-label Extension; MAD=multiple ascending dose; R=randomization.

3.2 Sample size justification

Assuming a 15% dropout rate, it is anticipated that approximately 60 subjects will be required to be randomized in order to achieve 51 evaluable subjects in the full analysis set (FAS). In Part A (Cohorts 1 - 3), the sample size is based on the feasibility of the safety and tolerability assessment to recommend starting the treatment of the next cohort of 12 subjects/cohort (9 subjects to receive KHK4083 and 3 subjects to receive placebo). In Part B (Cohort 4) for the treatment of 24 subjects (18 subjects to receive KHK4083 at the recommended dose based on the safety and tolerability in Part A and 6 subjects to receive placebo), the sample size is based on the feasibility of exploratory assessments in efficacy and safety at the recommended dose level. Based on the UCEIS and Mayo Clinic scores and from combining Part A and Part B, it is planned to have approximately a total of 27 randomized subjects receive the recommended dose of KHK4083 and 15 subjects receive placebo.

3.3 Randomization and blinding

After a subject meets all study eligibility requirements at Screening, the Interactive Response Technology (IRT) system will be used by the Investigator (or designee) to randomize the subject to double-blind Induction Therapy on Day 1 (Week 0). Subjects randomly assigned in Cohorts 1 - 3 will receive either KHK4083 (one of three dose levels) or placebo in a 3:1 ratio during Part A of Induction Therapy. Additional subjects (Cohort 4) in a 3:1 ratio will receive the recommended KHK4083 dose or placebo during Part B of Induction Therapy.

The subject, Investigator (or investigative site personnel) and KHK4083 study team at KKD will not know the treatment to which the subject is randomized during the double-blind Treatment Period. Placebo will be administered by IV infusion to each cohort to ensure blinded treatment. The study is being blinded to prevent bias in the safety evaluation, in particular the severity grading and causality determinations of AEs. However, at any time during the study, if a medical emergency occurs and subject treatment must be known, the blind may be broken according to the procedure described in protocol.

3.4 Efficacy endpoints

3.4.1 Primary endpoint

Subjects with moderately active UC will primarily be evaluated for an improvement in the mucosa determined by their mMES (subscores from 0 to 3, with modified endoscopy finding scoring, i.e., by excluding mild friability from a subscore of 1) at completion of double-blind Induction Therapy. The primary efficacy endpoint will be the mean change in the mMES from Baseline (Week 0) to Week 12 for all subjects who receive the recommended dose in Parts A and B.

3.4.2 Secondary efficacy endpoints

The secondary efficacy endpoints for all subjects who receive the recommended dose during double-blind Induction Therapy are as follows:

- Improvement in the mucosa at Week 12;
  – Changes in the mucosa will be based on the percentage of subjects with at least a 1-point improvement in their mMES (0 to 3) from Baseline (Week 0) to Week 12; and/or
  – Changes in the mucosa will be based on the percentage of subjects with at least a 1-point improvement in their modified Baron endoscopic score (5-point scale) from Baseline (Week 0) to Week 12; and/or
  – Changes in the mucosa will be based on the mean change in UCEIS (0 to 8) and subscores from Baseline (Week 0) to Week 12.

- Mucosal healing at Week 12;
  Mucosal healing is defined as a mMES of 0 or 1.
- Clinical improvement at Week 12;
  Improvement will be based on a reduction (mean change from Baseline [Week 0] at Week 12) in the total Mayo Clinic score (0 to 12).
- Clinical improvement at Weeks 2, 4, 6, 8, 10, and 12;
  Improvement will be based on mean changes from Baseline (Week 0) in the partial (excludes endoscopy subscores) Mayo Clinic score (0 to 10).
- Clinical response at Week 12;
  A clinical response is defined as a reduction in the total Mayo Clinic score of at least 3 points and a decrease of at least 30% from Baseline (Week 0) to Week 12, and a reduction in the rectal bleeding subscale of at least 1 point from Baseline (Week 0) to Week 12 or an absolute rectal bleeding score of 0 or 1 at Week 12.
- Clinical remission at Week 12;
  Clinical remission is defined as a total Mayo Clinic score of ≤ 2 and no subscores > 1.

For all subjects who receive KHK4083 at dose levels different than the recommended dose during double-blind Induction Therapy, improvement in the mucosa at Week 12 based on the mean change in the mMES from Baseline (Week 0) to Week 12 is the main secondary endpoint. The other secondary efficacy endpoints at Week 12 for all subjects who receive KHK4083 at other than the recommended dose are the same as those listed and defined above, i.e., improvement in the mucosa based on the modified Baron endoscopic score and the UCEIS; mucosal healing; clinical improvement based on total, as well as partial (excludes endoscopy subscore at Weeks 2, 4, 6, 8, 10, and 12) Mayo Clinic scores; clinical response; and clinical remission.

3.4.3 Exploratory efficacy endpoints

Efficacy exploratory endpoints will be included in this study for all subjects with moderately active UC who receive both Induction Therapy and OLE/LTE Therapy. The exploratory endpoints for all subjects who receive both Induction Therapy and OLE/LTE Therapy are as follows:

- Clinical improvement at Week 52;
  Improvement will be based on a reduction (mean change from Baseline [Week 0] to Week 52) in the total Mayo Clinic score (0 to 12).
- Clinical improvement at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 and at OLE/LTE Therapy Follow-up Period visits (Weeks 56, 60, and 64);
  Improvement will be based on mean changes from Baseline (Week 0) in the partial (excludes endoscopy subscores) Mayo Clinic score (0 to 10).
- Clinical response at Week 52;
  A clinical response is defined as a reduction in the total Mayo Clinic score of at least 3 points and a decrease of at least 30% from Baseline (Week 0) to Week 52, and a reduction in the rectal bleeding subscale of at least 1 point from Baseline (Week 0) to Week 52 or an absolute rectal bleeding score of 0 or 1 at Week 52.
- Clinical remission (i.e., a total Mayo Clinic score of ≤ 2 and no subscores > 1) at Week 52;
- Durable clinical responses and durable clinical remissions at Week 52 (i.e., present at both Week 12 and Week 52), and glucocorticoid-free clinical remission at Week 52;
- Mucosal healing (i.e., an mMES of 0 or 1) at Week 52;
- Improvement in the mucosa according to the following assessments:
  – At least a 1-point improvement in the mMES from Baseline (Week 0) to Week 52;
  – A mean change in the UCEIS score from Baseline (Week 0) to Week 52; and/or
  – At least a 1-point improvement in the modified Baron endoscopic score from Baseline (Week 0) to Week 52.
- Remission (i.e., mMES of 0 or 1, stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0) rates at Week 12 and Week 52;
- Improvement in the HRQL, which will be based on the subject's completed IBDQs;
- Lowered corticosteroid (glucocorticoid) dosages;
- Glucocorticoid-free treatment duration from Week 16 through Week 52, and through the OLE/LTE Therapy Follow-up Period (Week 56 through Week 64);

3.5 Safety endpoints

The safety and tolerability of KHK4083 will be determined by physical examination, vital signs, body weight, 12-lead ECGs, and clinical laboratory findings; and the number and percentage of subjects reporting AEs (frequency, severity, and relationship to investigational product), SAEs, and treatment discontinuation due to AEs.

3.6 Other endpoints

- PD profile of KHK4083
- PK-PD relationships

The analysis of PK, PD and immunogenicity data and parameters corresponding to those data are beyond the scope of this SAP. Separate analysis plans may be developed for these analyses.

4. Statistical Analysis

4.1 General

General descriptive statistics for continuous variables include the n (number of observed values), the mean, standard deviation, median, minimum, and maximum values. For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented. The percentage will be calculated using the subjects with a reported value. Counts of missing subjects will be identified for variables that had one or more subjects with a missing result. Descriptive statistics will be presented by treatment Cohort (KHK4083 dose levels; combined KHK4083; and placebo) and by visit.

Unless there are any notes, the following rules will be applied for all tables and figures;

- Data from placebo subjects in each Cohort will be combined, not depending on treatment period (Double-Blind Induction Therapy, Long-Term Extension Therapy, Open-Label Extension Therapy, or Follow-up).
- In the case that Screening or Baseline is necessary in the tables and figures related to LTE Therapy Period, OLE Therapy Period, or Follow-up Period, the data at Screening or Baseline will be used or displayed.
- Double-Blind Therapy Period will be defined as the period including both Double-Blind Induction Therapy Period and LTE Therapy Period.
- When “Week xx” (xx: number) is necessary, “Week xx” displayed on CRF will be used or displayed.

To explain how data are summarized, the figure showing the relationship between period and dose of Investigational Product is displayed in Figure 3 and the table defining the category is displayed in Table 2.

Figure 3 Relationship between Period and Dose of Investigational Product

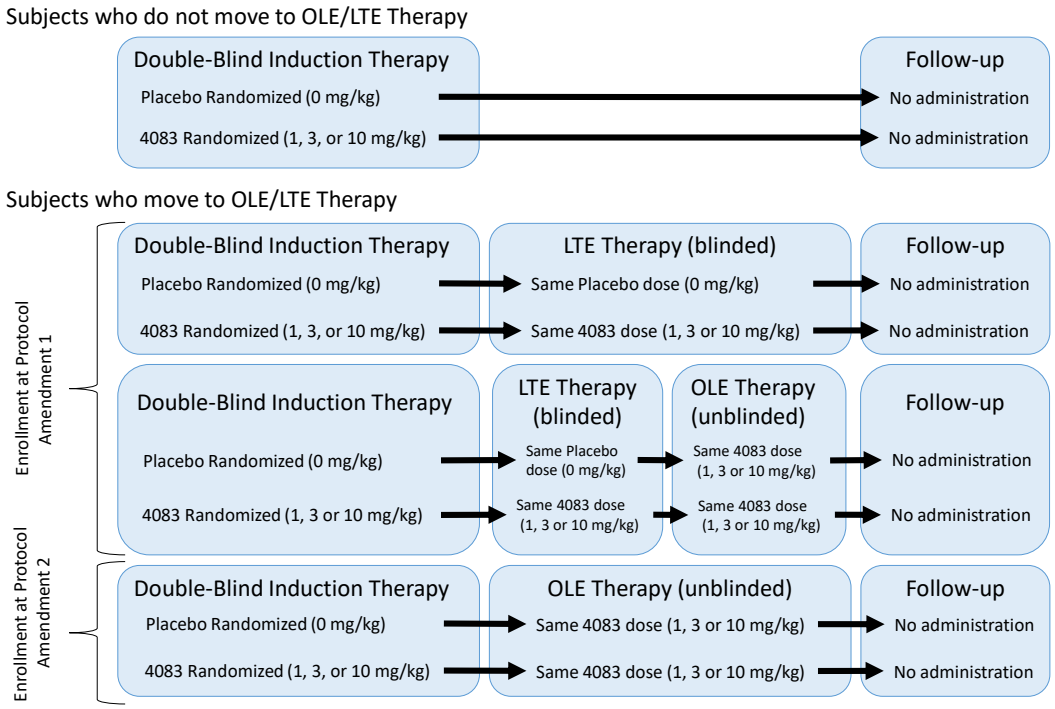


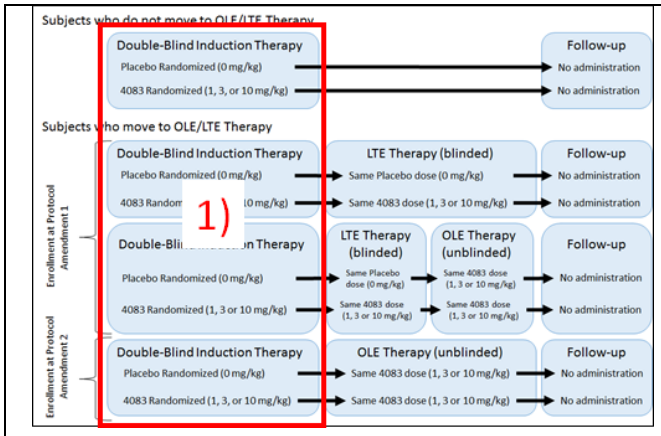
Table 2 Category in Tables and Figures

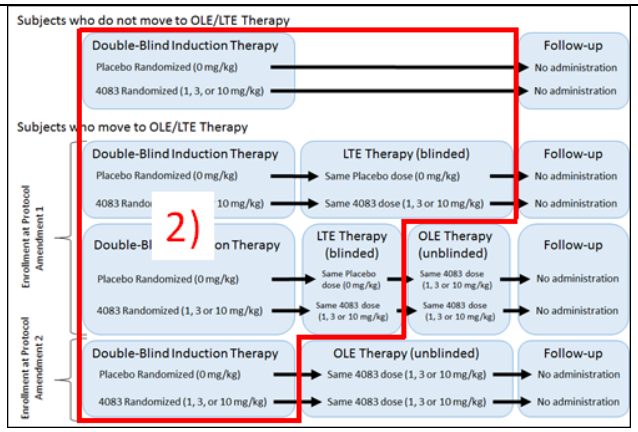
	4083 Randomized				Placebo Randomized			
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Summary Pattern	**Category In Tables and Figures**							
Double-Blind Induction Therapy Period Double-Blind Therapy Period [1)] Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period [2)] LTE Therapy Period LTE Therapy Period and Double-Blind Therapy Follow-up Period	1.0 mg/kg	3.0 mg/kg	10 mg/kg	1.0, 3.0 or 10 mg/kg	Placebo			
OLE Therapy Period OLE Therapy Period and OLE Therapy Follow-up Period	1.0 mg/kg	3.0 mg/kg	10 mg/kg	1.0, 3.0 or 10 mg/kg	Placebo [3)]			

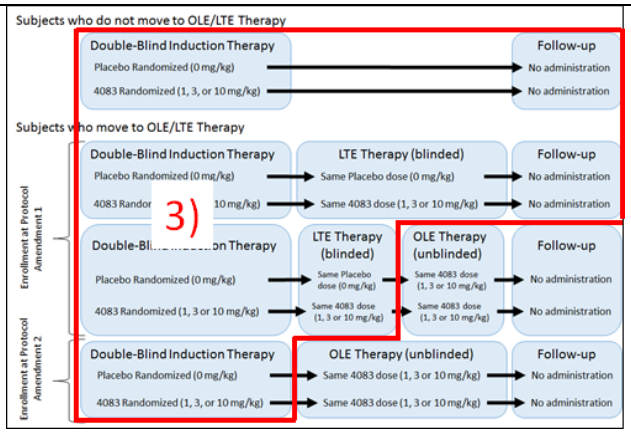
1) Double-Blind Therapy Period includes both Double-Blind Induction Therapy Period and LTE Therapy Period.
2) Double-Blind Therapy Follow-up Period includes both Follow-up Periods after Double-Blind Therapy Period and LTE Therapy Period.
3) For subjects randomized to Placebo, they receive 4083 administration during the duration but they are summarized as one category as "Placebo".

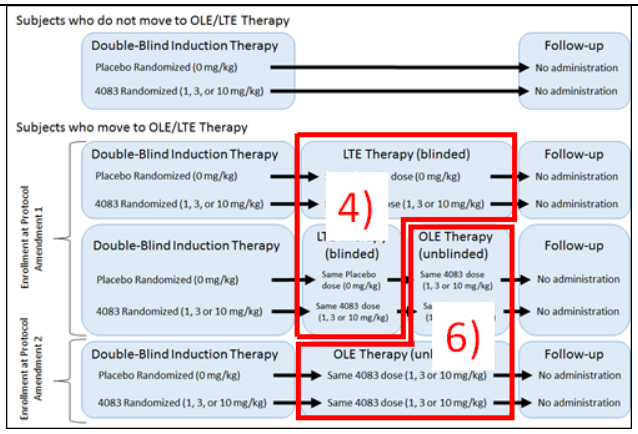
Image which shows the relationship between summary pattern and data will be displayed in Figure 4.

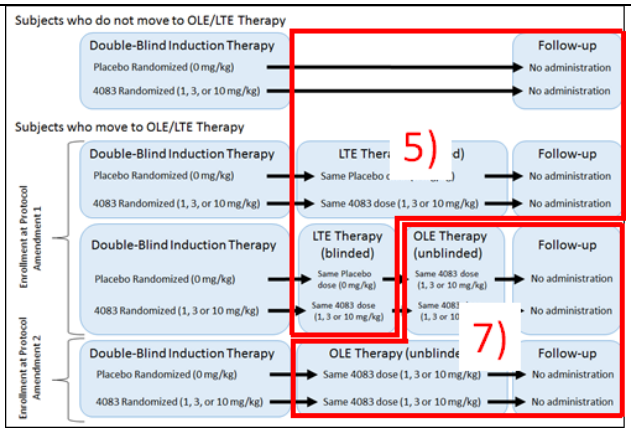
Figure 4 Summary Patterns











1) Double-Blind Induction Therapy Period

2) Double-Blind Therapy Period

3) Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period

4) LTE Therapy Period

5) LTE Therapy Period and Double-Blind Therapy Follow-up Period

6) OLE Therapy Period

7) OLE Therapy Period and OLE Therapy Follow-up Period

General reporting conventions will include the following:

- The baseline value for any measurement is the last value obtained prior to receiving administration of KHK4083 or placebo on Day 1 at Week 0. All nominal time points will be used for analysis; actual assessment times will not be used to reclassify the time point at which a measure was taken.

- Study day: Study day will be calculated relative to the date of KHK4083 or placebo administration (Day 1) as:
    - (If Date of event ≥ Date of first investigational product administration) Date of event – Date of first investigational product administration + 1 and
    - (If Date of event < Date of first investigational product administration) Date of event – Date of first investigational product administration

  This formula will be used when calculating days to a specific event (i.e., concomitant medication and/or AE start date). A negative study day indicates an event prior to investigational product administration.
- Unless otherwise noted, all percentages will be presented to one decimal place.
- Individual data listings of all data represented on the eCRF will be provided as an appendix to facilitate investigation of the tabulated values and to allow for the clinical review of all variables. All data listings will be sorted by dose Cohort, site-subject number, visit, and time points where appropriate.
- Post-dose data from unscheduled visits will be excluded from the summary tables but included in the data listings.

Statistical hypothetical testing will not be carried in this study. However, in the case that p-value is derived, it will be rounded to three decimal places.

All statistical analyses will be performed using Statistical Analysis System (SAS) statistical software (Version 9.2 or higher). AEs will be coded for summarization using Medical Dictionary for Regulatory Activities (MedDRA® Version 18.1). Concomitant medications will be coded using WHO Drug Dictionary (enhanced) 1st Q2015 B-format.

4.2 Analysis sets

Subjects will be screened to determine if they meet all inclusion and no exclusion criteria. Subjects will be analyzed according to the treatment they actually received. The following analysis sets will be used in the study:

- **Safety Analysis Set:** Includes all subjects who received any (even a partial dose) investigational product (KHK4083 or placebo); The Safety Analysis Set will be used to perform all safety analyses as the basis for all summaries proposed in this SAP.
- **Full Analysis Set (FAS)**: Includes all subjects who receive at least one full dose of investigational product and who have Baseline data and at least one post-treatment assessment of the primary efficacy variable. Summaries of efficacy will be presented for the FAS.

4.3 Covariates

All analysis of covariance (ANCOVA) models and linear Mixed Model will include the baseline value of the variable as a covariate and treatment as class type fixed effects.

4.4 Handling of missing and incomplete data

Available data at each time point will be presented. The denominator for percentages will be based on the number of subjects in the appropriate treatment or cohort group for summary purposes.

4.5 Changes in the planned analysis

The primary endpoint and main secondary endpoints of the study are based on 12 week Induction Therapy data. After the last subject completes Part B of Induction Therapy, the study will be unblinded. A cut with 12 week data will be applied. Baseline characteristics, prior/concomitant medication, 12-week efficacy data, 12-week AE data and 12-week exposure data will be cleaned before unblinding. The list of efficacy and safety tables that will be produced with results of 12 week Induction Therapy data is provided in Section 9.4.1. Results of these analysis will be used to make a determination on whether or not KHK4083 meets the criteria for proof of concept of efficacy. Subjects that were enrolled per Protocol Amendment 1 and continued to be blinded in the Long Term Extension period will remain blinded. Also investigators will remain blinded for these subjects.

4.6 Data Review Meeting

One data review meeting is planned before final database soft lock.

4.7 Software

Version 9.2 (or higher) of the SAS® statistical software package will be used to provide all summaries and data listings.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrollment and disposition

The number of Subjects screened and in each visit week will be presented by treatment Cohort. Subject disposition will be summarized including the number and percentage of subjects enrolled and completed each of the study periods (Double-Blind Induction Therapy Period, Doubld-Blind Induction Therapy Follow-up Period, OLE/LTE Therapy Period, and OLE/LTE Therapy Follow-up Period), discontinued from the treatment, discontinued the study and completed the study. The number of subjects who moved from LTE to OLE Therapy Period. The definitions for completions and discontinuations are shown below;

- Subjects who have the CRF page of "Week 12" will be defined as those who completed Induction Therapy.
- Subjects who have the CRF page of "Follow-up 3 - Subjects not enrolling in LTE Therapy Period" or "Follow-up 3 - Subjects not enrolling in OLE Therapy Period" will be defined as those who completed Double-Blind Induction Therapy Follow-up Period.
- Subjects who have the CRF page of "Week 52" will be defined as those who completed OLE/LTE Therapy Period.
- Subjects who have the CRF page of "Follow-Up 3 - Post Long Term Extension Therapy" will be defined as those who completed OLE/LTE Therapy Follow-up Period.
- Subjects who have the CRF page of "End of treatment" will be defined as those who discontinued the treatment.
- Subjects who have "No" for the question of "Did the subject complete the study?" on the CRF page of "End of study" will be defined as those who discontinued the study.
- Subjects who have "Yes" for the question of "Did the subject complete the study?" on the CRF page of "End of study" will be defined as those who completed the study.

The number of subjects in the Safety Analysis Set and FAS will be provided. Disposition information will be provided overall and separately for each treatment Cohort.

The reasons why subjects were excluded from any analysis set will be listed individually.
In addition table summaries of the primary reason for discontinuation/withdrawal from the study will be presented by means of number and percentage of subjects by treatment cohort, period and overall.

5.2 Protocol deviations

Before unblinding, investigator and KKD will address all protocol deviations highlighted during the study a list will be presented in addition to a summary of the major and minor deviations from the protocol.

5.3 Demographics and baseline characteristics

Demographic characteristics (including age, race, ethnicity, and sex), height, weight, BMI (where BMI = Body weight (kg)/Height (m)^2), duration of UC diagnosis, and Baseline values for UC assessment will be summarized by treatment Cohort using descriptive statistics in the Safety Analysis Set.

The following UC assessments scores will be provided:

1. Each subscore (for Mayo Clinic Score (0 to 3 for each subscore)
    a. Stool frequency
    b. Rectal bleeding
    c. Modified Mayo endoscopy subscore (mMES)
    d. Physician's global assessment
2. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) Score (0 to 8)
3. Modified Baron Endoscopic Score (0 to 4)
4. Total Mayo Clinic Score (0 to 12) is the sum of stool frequency (subscore 0 to 3), rectal bleeding (subscore 0 to 3), mMES (subscore 0 to 3) and physician's global assessment (subscore 0 to 3).
5. Partial Mayo Clinic Scores (0 to 9) is the Complete Mayo Clinic Score without the mMES.
6. Total Inflammatory Bowel Disease Questionnaire (IBDQ) score is a quality-of-life assessment at Baseline. It is the sum of IBDQ Sub Scores.
7. Four IBDQ Sub Scores include bowel-related symptoms, systemic function, social function, and emotional status.

No statistical comparisons of differences in demographics/baseline data will be performed.
Data listings will also be provided for all demographic information and baseline characteristics.

5.4 Medical, diet and surgical history

Medical history and concomitant diseases will be coded using MedDRA (version 18.1) and frequency distributions and percentages will be summarised by sequence for the Safety Analysis Set by System

Organ Class (SOC) and Preferred Term. Medical history will be defined as the event that the answer for the question of "Ongoing at time of Informed Consent" on the CRF page of "Medical/Surgical History" is "No". Concomitant disease will be defined as the event that the answer for that question is "Yes".

Medical/surgical history and physical examination results of note, will also be listed by subject.

5.5 Prior and concomitant medications

Start and stop dates of medication or non-drug therapy will be compared to the start date of investigational product dosing to allow medications/treatments to be classified as either *prior* or *concomitant*.

Prior medications include any previous biologic treatment (for any indication), all treatment for UC taken within 6 months prior to Screening, and any other previous medication taken within 1 month prior to Screening. Concomitant medications include medications that started at any time and were taken at any time during the study including the follow-up period. Probiotic usage is to be tracked during the study.

If a start or stop date of medication or non-drug therapy is partial, the date will be compared as far as possible with the investigational product dosing start date. The medication or non-drug therapy will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication stopped prior to the investigational product dosing start date. If the stop dates are missing, medications will be assumed to be concomitant.

The World Health Organization Drug Dictionary will be used to classify prior and concomitant medications by Therapeutic Class and Preferred Term. Prior medications will be summarized in the Safety Analysis Set. Concomitant medications will be summarized by each period (Double-Blind Induction Therapy Period, OLE Therapy Period, LTE Therapy Period, or Follow-up Period) in the Safety Analysis Set.

6. Evaluation of Treatment Exposure

6.1 Exposure to investigational product

Subjects who received investigational product are those who have the infusion initiation time recorded, and subjects who completed investigational product are those who have the completion time recorded. The definition of treatment duration in weeks will be derived from the recorded date and time of the IV infusion of investigational product as follow:

- Induction therapy: IV infusion of KHK4083 or placebo once every 2 weeks for a total of 6 treatments. For eligible subjects the first dose date for the Induction therapy is recorded at Day 1 (Week 0) after screening period; the last recorded dose date for the Induction therapy should be recorded at Day 71 (Week 10). Under this condition the treatment duration for the Induction

therapy is derived as [(last dose date of the Induction therapy - first dose date of the induction therapy)+1]/7, and the results will be expressed in weeks and rounded to the nearest integer.

- Long-term Extension Therapy (LTE): all the subjects who qualify and agreed to continue the treatment will receive 10 additional IV infusions of KHK4083 or placebo once every 4 weeks starting from Week 12 (+/- 7 days). Under this condition the treatment duration for the LTE therapy is derived as [(last dose date - first dose date of the LTE therapy)+1]/7, and the results will be express in weeks and rounded to the nearest integer.
- Open-label Extension Therapy (OLE): all the subjects who qualify and agreed to continue the treatment will receive up to10 additional IV infusions of KHK4083 once every 4 weeks starting from the first dose of the OLE therapy ["Week" of the first dose of the OLE therapy is different among subjects: Week 12 (+/- 7 days), Week 16 (+/- 7 days), Week 20 (+/- 7 days), Week 24 (+/- 7 days), or Week 28 (+/- 7 days)]. Under this condition the treatment duration for the OLE therapy is derived as [(last dose date - first dose date of the OLE therapy)+1]/7 results will be expressed in weeks and rounded to the nearest integer.
- Overall: for subjects who had completed the Induction therapy and continued to the OLE or LTE therapy, the overall treatment duration under each investigational product administered will be derived as [(last dose date - first dose date)+1]/7, and the results will be expressed in weeks and rounded to the nearest integer.

The total dose administration is the sum of investigational product administered. The cumulative administered volume is the sum of dose of investigational product administered. Both the total administration and the cumulative administered volume will be derived by each treatment period (Double-Blind Induction Therapy Period, LTE Therapy Period, OLE Therapy Period, and Overall) as well as the duration of treatment.

Total dose administered, duration of treatment, and cumulative administered volume will be summarized by each treatment period (Double-Blind Induction Therapy Period, LTE Therapy Period, OLE Therapy Period, and Overall).

6.2 Evaluation of pharmacokinetics

The analysis and reporting of PK data and parameters are beyond the scope of this SAP. A separate analysis plan is planned to be developed for this analysis and a final report will be provided under separate cover.

6.3 Evaluation of immunogenicity

The analysis and report of Anti-drug antibody will be provided under separate cover as well as PK.

7. Evaluation of Efficacy

The efficacy endpoints will be evaluated in FAS population and results will be presented in listings and tables. Continuous variables will be tabulated with descriptive statistics. Categorical measures will be summarized as number and percentage of subjects.

7.1 Analysis of primary endpoint

The primary efficacy endpoint is the mean change in mucosal score presented by mMES (subscores from 0 to 3 with modified endoscopy finding scoring, i.e., excluding mild friability from a subscore of 1) from Baseline (Week 0) to Week 12 for all subjects who received the recommended dose during Induction Therapy. This includes Part A subjects who received the recommended dose identified for Part B as well as the subjects who received the recommended dose during Part B of Induction Therapy. Change from Baseline in mMES as well as Baseline and Week 12 will be summarized by treatments (each KHK4083 dose level and placebo) by means of descriptive statistics (number of subject n, mean, standard deviation, median, min and max); the 95% confidence Interval (CI) for the change from baseline will be derived as follow:

Upper 95%CI = $\mu_x + t(\alpha,df)SE(\mu_x)$

Lower 95%CI = $\mu_x - t(\alpha,df)SE(\mu_x)$

where:

- μ_x is the arithmetic mean estimate of the change from baseline
- t is the value from a t table distribution with $\alpha = 0.05$ and df degree of freedom

SE is the Standard error of the mean estimate.

A comparison between treatments (each KHK4083 dose level versus placebo) will be performed using an ANCOVA model with change from Baseline in mMES as dependent variable and treatment as fixed effect and baseline value as covariate. The number of subjects and the number of subjects considered in the model will be provided by treatment. The adjusted means for treatments (least squares means) and the relative 95% CIs will be presented. The difference between the adjusted means for each treatment groups from placebo (Difference in Least Squares Mean from Placebo) will be calculated with the relative 95% CI and p-value. Least squares means with 95% CIs and differences in least squares mean from placebo with 95% CIs will be graphically presented.

In order to test for optimal dose levels within this fitted linear model, three types of contrasts will be defined to demonstrate which KHK4083 dose level is deemed closest to optimal. The first contrast is for the scenario of "10 mg/kg is closest to optimal" and its vector, (P L M H), is (-1 -1 -1 3), where P: Placebo; L: 1.0 mg/kg; M: 3.0 mg/kg; and H: 10 kg/mg. The second contrast is for the scenario of "3.0 mg/kg is closest to optimal" and its vector is (-1 -1 1 1). The third contrast is for the scenario of "1.0 mg/kg is closest to optimal" and its vector is (-3 1 1 1). Each contrast will be tested within the fitted model to determine the dose level providing optimum benefit over placebo.

SAS® code

```
Proc GLM data=dataset;
Class tmt;
Model change=tmt baseline / solution clparm;
```

```
Lsmeans tmt/cl stderr;
Estimate "1.0 mg Vs Placebo" tmt  -1 1 0 0;
Estimate "3.0 mg Vs Placebo" tmt  -1 0 1 0;
Estimate "10 mg Vs Placebo"  tmt  -1 0 0 1;
Contrast "1.0 mg is closest to optimal" tmt   -3  1  1  1;
Contrast "3.0 mg is closest to optimal" tmt   -1 -1  1  1;
Contrast "10 mg is closest to optimal"  tmt   -1 -1 -1  3;
Run;
```

7.2 Analysis of secondary efficacy endpoints

The secondary efficacy variables for all subjects (i.e., recommended dose or any other dose level in Parts A and B of Induction Therapy) are listed in the following table.

Efficacy Variables	Definition
Improvement in the Mucosa (Measured by modified Mayo endoscopy subscore [mMES]) (Week 12)	Percentage of subjects with at least a 1-point improvement in their mMES (0 to 3) from Baseline (Week 0) to Week 12.
Improvement in the Mucosa (Measured by modified Baron scoring system) (Week 12)	Percentage of subjects with at least a 1-point improvement in their modified Baron endoscopic score (5-point scale) from Baseline (Week 0) to Week 12.
Improvement in the Mucosa (Measured by Ulcerative Colitis Endoscopic Index of Severity [UCEIS]) (Week 12)	A mean change in the UCEIS (scores from 0 to 8, based on findings of vascular pattern, bleeding, and erosions/ulcers) from Baseline (Week 0) to Week 12.
Mucosal Healing (Week 12)	The percentage of subjects with mMES of 0 or 1 at Week 12.
Clinical Improvement (Week 12)	Mean change from Baseline (Week 0) at Week 12, in the total Mayo Clinic score (0 to 12).
Clinical Improvement (Weeks 2, 4, 6, 8, 10, and 12)	Mean changes from Baseline (Week 0) in the partial (excludes endoscopy subscores) Mayo Clinic score (0 to 10).
Clinical Response (Week 12)	A reduction in the total Mayo Clinic score of at least 3 points and a decrease of at least 30% from Baseline (Week 0) to Week 12, and a reduction in the rectal bleeding subscale of at least 1 point from Baseline (Week 0) to Week 12 or an absolute rectal bleeding score of 0 or 1 at Week 12.
Clinical Remission (Week 12)	A total Mayo Clinic score of ≤ 2 and no subscores > 1.

All secondary efficacy variables will be summarized by treatments (each KHK4083 dose level and placebo). Change from Baseline in UCEIS, total Mayo Clinic score as well as Baseline and Week 12 will be summarized by treatments. Partial Mayo Clinic scores and changes from Baseline will be summarized from Baseline to Week 12 by treatments. Summaries statistics and 95% CI will be presented and estimated as described in section 7.1 of this SAP.

A comparison between treatments (each KHK4083 dose level versus placebo) will be performed using an ANCOVA model with changes from Baseline in UCEIS, total Mayo Clinic score and partial Mayo Clinic score at Week 12 as dependent variables, treatment as fixed effect and baseline value as covariate. The number of subjects and the number of subjects considered in the model will be provided by treatment. The adjusted means for treatments (least squares means) and the relative 95% CIs will be presented. The difference between the adjusted means for each treatment groups from placebo (Difference in Least Squares Mean from Placebo) will be calculated with the relative 95% CI and p-value. Least squares means with 95% CIs and differences in least squares mean from placebo with 95% CIs will be graphically presented.

7.3 Analysis of exploratory efficacy endpoints

All exploratory efficacy variables will be summarized by treatments. The changes from Baseline in mMES, UCEIS and total Mayo Clinic score as well as Baseline and Week 52 will be summarized by treatments. In addition, the partial Mayo Clinic scores (without sigmoidoscopy) and changes from Baseline will be summarized by study visit at Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 and at OLE/LTE Therapy Follow-up Period visits (Weeks 56, 60, and 64).

The change from Baseline in HRQL based on IBDQ will be analyzed for total score and 4 subscale scores at all study visits (Weeks 2 to 52, including Induction Therapy Follow-up Period visits (Weeks 16, 20, and 26) and OLE/LTE Therapy Follow-up Period visits (Weeks 56, 60, and 64).

Remission (mMES of 0 or 1, stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0) rates at Week 12 will be summarized. Remission rates at Week 52 will be summarized by Double-Blind Period and OLE Therapy Period as well.

Clinical response and clinical remission will be summarized at Week 52. The percentage of subjects with mucosal healing, and the percentages of subjects with improvement in the mucosa (change from Baseline of at least a 1-point improvement in the mMES and/or in the modified Baron endoscopic scores) at Week 52 will be summarized by Double-Blind Period and OLE Therapy Period.

Durable clinical response and durable clinical remission at Week 52 will be summarized by Double-Blind Period and OLE Therapy Period. Durable clinical response and durable clinical remission at Week 52 will be defined as follows:

- Duration clinical response at Week 52 will be defined in the case that clinical response is present at both Weeks 12 and 52.
- Duration clinical remission at Week 52 will be defined in the case that clinical remission is present at both Weeks 12 and 52.

Glucocorticoid-free clinical remission at Week 52 will be summarized by Double-Blind Period and OLE Therapy Period. At Weeks 16 through 52 and through the OLE/LTE Therapy Follow-up Period (Week 56 through Week 64), the change from baseline in corticosteroid (glucocorticoid) dosages and the duration of glucocorticoid-free treatment will be summarized. Those parameters definitions are shown below.

- Glucocorticoid-free clinical remission at Week 52
    - Glucocorticoid-free clinical remission at Week 52 will be defined in the case that clinical remission is present at Week 52 and no glucocorticoid listed in Section 9.3 is used from Week 16 through Week 52.
- Glucocorticoid dosages:
    - Baseline glucocorticoid dosages (times) will be defined as the total number of administrations of glucocorticoid listed in Section 9.3 that is used during Double-Blind Induction Period (from Day 1 to a day before Week 16). For the subject who receives no glucocorticoid, the dosages will be 0.

- Glucocorticoid dosages (times) at Week 16 through Week 52 will be defined as the total number of administrations of glucocorticoid listed in Section 9.3 that is used during OLE/LTE Therapy Period (from Week 16 to Week 52). For the subject who receive no glucocorticoid, the dosages will be 0.
- Glucocorticoid dosages (times) at Week 16 through LTE Therapy Follow-up Period will be defined as the total number of administrations of glucocorticoid listed in Section 9.3 that is used during LTE Therapy Period and LTE Therapy Follow-up Period (from Week 16 to Follow-up 3). For the subject who receives no glucocorticoid, the dosages will be 0.
- Glucocorticoid dosages (times) at Week 16 through OLE Therapy Follow-up Period will be defined as the total number of administrations of glucocorticoid listed in Section 9.3 that is used during OLE Therapy Period and OLE Therapy Follow-up Period (from Week 16 to Follow-up 3). For the subject who receives no glucocorticoid, the dosages will be 0.
- If there is glucocorticoid that the number of administrations is unknown, it will be assumed that the glucocorticoid was used at a frequency of an administration per day.
- For the subjects who do not move to OLE/LTE Therapy Period, "Glucocorticoid dosages (times) at Week 16 through Week 52" and "Glucocorticoid dosages (times) at Week 16 through OLE/LTE Therapy Follow-up Period" will not be defined.

- Change from baseline in corticosteroid (glucocorticoid) dosages will be defined as follows:
  - Change from baseline in corticosteroid (glucocorticoid) dosages at Week 16 through Week 52 = Glucocorticoid dosages at Week 16 through Week 52 - Baseline glucocorticoid dosages
  - Change from baseline in corticosteroid (glucocorticoid) dosages at Week 16 through LTE Therapy Follow-up Period = Glucocorticoid dosages at Week 16 through LTE Therapy Follow-up Period - Baseline glucocorticoid dosages
  - Change from baseline in corticosteroid (glucocorticoid) dosages at Week 16 through OLE Therapy Follow-up Period = Glucocorticoid dosages at Week 16 through OLE Therapy Follow-up Period - Baseline glucocorticoid dosages
- Duration of glucocorticoid-free treatment will be defined as the duration that no glucocorticoid listed in Section 9.3 is used from Week 16 through Follow-up 3.
  - Duration of glucocorticoid-free treatment (days) = Date of first glucocorticoid after Week 16 visit - Date of Week 16 visit
  - If the subject received glucocorticoid on the date of Week 16 visit, the duration of glucocorticoid-free treatment for the subject is 0.

A comparison between treatments (each KHK4083 dose level versus placebo) will be performed using an ANCOVA model with changes from Baseline in UCEIS, total Mayo Clinic score and partial Mayo Clinic score at Week 52 during Double-Blind Therapy Period as dependent variables, treatment as fixed effect and baseline value as covariate. The number of subjects and the number of subjects considered in the model will be provided by treatment. The adjusted means for treatments (least squares means) and the relative 95% CIs will be presented. The difference between the adjusted means for each treatment groups from placebo (Difference in Least Squares Mean from Placebo) will be calculated with the relative 95% CI and p-value. If ANCOVA cannot be applied

due to the issue that the parameters cannot be estimated appropriately, these analyses using ANCOVA for Week 52 will not be applied.

Means with SDs for the efficacy variables (mMES, UCEIS, total Mayo score and partial Mayo score) at all visits will be performed graphically by each treatment (e.g. Placebo, 1.0 mg/kg, 3.0 mg/kg, or 10 mg/kg) and by Double-Blind Therapy Period and OLE Therapy Period. For partial Mayo score, Means with SDs as all visits will be performed graphically by "Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period" and "OLE Therapy Period and OLE Therapy Follow-up Period". Mean changes from Baseline will also be performed in the same manner.

To take into consideration about the repeat measurements in partial Mayo Clinic score, an analysis using a Mixed Model for Repeated Measures (MMRM) will be performed. A comparison between treatments (each KHK4083 dose level versus placebo) will be performed using a MMRM with the change from baseline in partial Mayo Clinic scores during Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period as dependent variable, treatment as fixed effect and baseline value as covariate, and visit as random effects. The interaction between treatment and visit also will be included. An unstructured covariance matrix will be considered and the Kenward-Roger adjustment will be used for the degrees of freedom. In the case that the unstructured covariance matrix cannot be used, a compound symmetry will be used as the covariance matrix instead of the unstructured one. The number of subjects, the number of subjects considered in the model and the number of observations considered in the model will be provided by treatments. The adjusted means for treatments (least squares means) at each visit and the relative 95% CIs will be presented. The differences between the adjusted means for treatments from placebo (Difference in Least Squares Mean from Placebo) at each visit will be calculated with the relative 95% CIs and p-values. If MMRM cannot be applied due to the issue that the parameters cannot be estimated appropriately, the structure of covariance matrix will be changed to compound symmetry. If MMRM cannot be applied by using the covariance matrix of compound symmetry, this analysis using MMRM will not be applied.

SAS® code

```
proc mixed data=dat001 ORDER=DATA;
  class visit tmt;
  model chg=tmt visit baseline tmt*visit /solution ddfm=kr;
  repeated visit / type=un subject= subjectj;
  lsmeans tmt*visit / slice=tmt pdiff diff alpha=0.05 cl;
  lsmeans tmt / pdiff diff alpha=0.05 cl;
run;
```

For the following scores, to show changes in score during the study, those scores will be summarized by treatments.

- Subscores of Mayo Clinic Score other than mMES: "Stool Frequency", "Rectal Bleeding", and "Physician's Global Assessment"
- Modified Baron Endoscopic Score
- Subscores of UCEIS: "Vascular pattern", "Bleeding", and "Erosions and ulcers"

To show the differences between Investigational products in each cohorts, the efficacy variables (mMES, UCEIS, total Mayo score and partial Mayo score) at all visits will be summarized by treatments and cohorts.

7.4 Evaluation of pharmacodynamics

The analysis of PD data and parameters are beyond the scope of this SAP. Separate analysis plans may be developed for these analyses. In this SAP only listing of the following PD parameters is planned:

- Fecal calprotein.
- wr-CRP
- delayed type hypersensitivity skin testing

8. Evaluation of Safety

All analysis of safety will be performed using the Safety Analysis Set.

Results of all safety assessments, including physical examinations, body weight, vital sign determinations, AE monitoring, ECGs, and clinical laboratory evaluations, will be summarized with descriptive statistics by dose Cohort and overall, and/or presented in data listings.

8.1 Adverse events

The onset date of an adverse event will be compared to the date of investigational product dosing to determine if the adverse event is treatment-emergent or not. Adverse events with an onset date on or after the first date of investigational product dosing will be classified as treatment emergent adverse events (TEAEs). If the adverse event onset date is missing or partial, the date will be compared as far as possible with the date of investigational product dosing. Adverse events will be assumed to be TEAEs unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to receiving the dose of investigational product.

TEAE will be summarized in a table that presents the number and percentage of subjects with any TEAE, with any serious TEAE, with any drug-related TEAE, with any TEAE leading to discontinuation and death overall and within each treatment period (Double-Blind Induction Therapy Period, LTE Therapy Period, and OLE Therapy Period) by treatments (each KHK4083 dose level versus placebo). It will also include the total number of adverse events in each of these categories. All TEAEs will be summarized showing the number and percentage of subjects for each event with a start time within the treatment period (i.e., Double-Blind Induction Therapy Period, LTE Therapy Period, and OLE Therapy Period) and by treatments (each KHK4083 dose level versus placebo) during Induction Therapy or KHK4083 dose level versus placebo during OLE /LTE Therapy Period. All TEAEs will be summarized by SOC and Preferred Term as well as by Preferred Term in decreasing frequency. Two additional summary tables are presented for serious TEAEs and Related TEAEs.

Listings of all adverse events (including non-treatment-emergent events) will be provided. This listing will be presented by dose cohort and will include site-subject identifier, adverse event (SOC, Preferred Term, reported term), start date, stop date, study day, severity grade, seriousness, relationship to drug, action taken with study treatment, and outcome. Also SAEs will be listed in a similar format as described above. Deaths which are adverse events leading to death, adverse events leading to discontinuation and adverse events with withdrawal of investigational product also will be listed in the same manner.

8.2 Clinical laboratory evaluation

Laboratory values (chemistry, hematology, coagulation profile, and urinalyses) will be numerically described by visit for observed values and change from baseline by treatments (each KHK4083 dose level versus placebo). The numbers and percentages of subjects with high, normal and low laboratory results will be also summarized for each visit by treatments (Placebo, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg) and treatment periods ("Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period" and "OLE Therapy Period and OLE Therapy Follow-up Period"). For the laboratory values which have the normal (e.g., below/within above the normal range) or categorical result (e.g., −/±/+), shift tables will display the cross tabulation of the baseline versus the results of the post-baseline by treatments (Placebo, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg) and treatment periods ("Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period" and "OLE Therapy Period and OLE Therapy Follow-up Period").

Means with SDs for numeric parameters among lab values at all visits will be performed graphically by treatments. Mean changes from Baseline will also be performed in the same manner.

Data listings will be generated of all safety lab values that are outside of the normal range. Listing will also be prepared for multiplex-31 assay data.

8.3 Vital signs and body weight

Vital signs, including systolic and diastolic blood pressures (mm Hg), radial pulse rate (beats/min), and respiration rate (breaths/min), oral body temperature (degrees Celsius), and body weight (kg) will be summarized descriptively by time point of collection for the data as observed. Change from baseline results will be summarized in the same manner as the laboratory values.

8.4 ECGs

Electrocardiogram measurements include heart rate (beats/min), RR interval (msec), PR interval (msec), QRS duration (msec), QT interval (msec), QTc interval (msec) and ECG interpretation. A standard 12-lead ECG will be performed at Screening; during Induction Therapy (predose and at the end of infusion) on Day 1 (Baseline, Week 0), Week 8, and Week 10 and at Week 52 of OLE/LTE Therapy Period. The ECGs will be recorded after the subject has rested for approximately 5 minutes in a supine position.

Summary statistics for the actual ECG parameter values and change from baseline will be provided for each visit. The number and percentage of subjects with elevated QTcF values (> 450 msec, > 480 msec, and > 500 msec) at each scheduled visit (time point) and overall for all post-baseline visits will be presented by treatments (each KHK4083 dose level versus placebo). In addition, the number and percentage of subjects with QTcF values that increase by > 30 msec and > 60 msec from baseline will be presented by treatments at each scheduled visit (time point) and overall for all post-baseline visits. QTcF will be calculated by the Fridericia formula that "(QTcF = QT/(RR)1/3)".

A shift table from baseline to the worst post-baseline values during the treatment period will be provided for QTcF interval. Both scheduled and unscheduled visits during the treatment period will be considered. The following categories will be used: ≤ 450 msec, > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and > 500 msec.

The numbers and percentages of subjects with reported 'Abnormal, Clinically Significant Change' ECG results will be also summarized for each visit by treatments (Placebo, 1.0 mg/kg, 3.0 mg/kg, and 10 mg/kg) and treatment periods ("Double-Blind Therapy Period and Double-Blind Therapy Follow-up Period" and "OLE Therapy Period and OLE Therapy Follow-up Period").

All ECG parameters will be presented in data listings.

8.5 Physical examination except body weight

The complete physical examination will include examination of all pertinent body systems while the subsequent physical examinations will include specific assessments of any changes from previous status and review of those organ systems as deemed appropriate for that subject. Physical examination results will be included in individual subject listings.

9. Tables and Listings

9.1 Programs and tables quality control

The statistical programmer of the tables and listings will carefully review the programs and will verify that no error message is highlighted in the 'LOG' file. Moreover, a second statistical programmer will verify the internal consistency of each table by checking the results using different SAS programs.

The following level of validation will be implemented:

Validation of statistical datasets: independent programming, with a comparison of the results against the initial datasets.

Validation of statistical output: independent programming, with a comparison of the results against the initial output.

9.2 Programming conventions

All tables/listings will be presented in landscape format.
The standard font size is 9 points Courier New for all tables. Listings will be presented with an 8 or 7 points Courier New.

Titles will be center-aligned; footnotes will be left-aligned.
Each table/figure/listing will have 2 titles:

- The 1st title will be the table/figure/listing number with the description of the table/figure /listing;
- The 2nd title will be a description of the study population presented in the table/figure/listing.

Some tables will have another title (before 2nd title) with a description of the statistical method used in those tables.

Any footnote added to explain the table/listing/figure contents will be presented in the following format:
Note 1: Percentages are calculated on the number of subjects (N).
Note 2: A serious adverse event is an....
Note 3: …….

The last two footnotes of each table/figure will be footers indicating:

- the reference listing of the data;
- the program name, the date and time of generation and the SAS® version used.

The last footnote of each listing will be a footer indicating the program name, the date and time of generation and the SAS® version used.

In the tables and listing the treatment under comparison will be labeled as “Cohort 1 1.0 mg/kg”, ‘Cohort 2 3.0 mg/kg’ “Cohort 3 10 mg/kg”, ‘Cohort 4 XX mg/kg’ (XX is the recommended dose) and “Placebo”.

In tables and figures, unless otherwise stated, the number of subjects corresponding to analysis set will be shown at the part of “N=XX” together with the labels of treatment group.

- For example, in Table 14.3.1-1.1 “Overall summary of treatment-emergent adverse events during study / safety analysis set”, the part of “N=XX” will display the number of subjects in safety analysis set corresponding to the labels of the treatment group (e.g. 1.0 mg/kg, 3.0 mg/kg, 10 mg/kg, Placebo) and All.

Unless otherwise stated, listings will be presented by randomized treatment, and sorted by cohort and the site-subject identifier.

Except for the listings 16.2.1-1.2 (based on screening failure subjects) and 16.2.1-1 (based on all subjects), all the listings will be based on the randomized subjects.

In all the listings on safety variables, a column with a flag (§) for treatment misallocation will identify the treatment misallocations.
The derived variables will be identified in the listings with a flag (*).

Tabular display of data for prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, drug class, or SOC with the highest occurrence in the active treatment group (KHK4083 combined group) in decreasing order. Within the body system, drug class and SOC, medical history (by Preferred Term), drugs (by ATC1 code), and adverse events (by Preferred Term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes. Numeric variables will be listed generally with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses approximations will not be performed):

- Age (years), duration of treatment (days): 0 decimal place;
- Change from baseline: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data;
- Mean and its confidence limits (unadjusted and adjusted), adjusted difference between means and its confidence limits, SD, median: actual data + 1 decimal;
- Percentage: 1 decimal place.

9.3 Glucocorticoid

Among concomitant medications which started to be administered from Day 1, those corresponding to the list below will be defined as glucocorticoid and considered in Tables and Listings relative to glucocorticoid.

- Medications that ATC code is “H02AB” (that is assigned to “Glucocorticoids”).

9.4 Tables

Number	Title
Table 14.1-1	Disposition of Subjects / Summary of All Subjects
Table 14.1-2.1	Demographic Characteristics / Safety Analysis Set
Table 14.1-2.2	Baseline Assessment of Ulcerative Colitis / Safety Analysis Set
Table 14.1-2.3	Demographic Characteristics / Full Analysis Set
Table 14.1-2.4	Baseline Assessment of Ulcerative Colitis / Full Analysis Set
Table 14.1-3.1	Prior Medications / Safety Analysis Set
Table 14.1-3.2	Concomitant Medications During Induction Period / Safety Analysis Set
Table 14.1-3.3	Concomitant Medications During Double-Blind Long Term Extension and Follow-Up Therapy / Safety Analysis Set
Table 14.1-3.4	Concomitant Medications During Open-Label Extension Therapy Period and Follow-Up Therapy / Safety Analysis Set
Table 14.1-4.1	Medical and Surgical History / Safety Analysis Set
Table 14.1-4.2	Concomitant Diseases / Safety Analysis Set
Table 14.1-5	Exposure to Investigational Product During Induction Therapy Period / Safety Analysis Set
Table 14.1-6	Exposure to Investigational Product During Long-Term Extension Therapy Period / Safety Analysis Set
Table 14.1-7	Exposure to Investigational Product During Open-Label Extension Therapy Period / Safety Analysis Set
Table 14.1-8	Exposure to Investigational Product During Study / Safety Analysis Set
Table 14.2-1.1	Summary of Baseline and Change from Baseline of Modified Mayo Endoscopy (MMES) / Full Analysis Set
Table 14.2-1.2	Change from Baseline in MMES at Week 12 / Full Analysis Set
Table 14.2-2.1	UCEIS During Induction Therapy Period / Full Analysis Set
Table 14.2-2.2	Total Mayo Clinic Score at During Induction Therapy Period / Full Analysis Set
Table 14.2-2.3	Partial Mayo Clinic Score at During Induction Therapy Period / Full Analysis Set
Table 14.2-2.4	Clinical Improvement at Week 12 / Full Analysis Set
Table 14.2-2.5.1	Change from Baseline in UCEIS at Week 12 / Full Analysis Set
Table 14.2-2.5.2	Change from Baseline in Total Mayo Clinic Score at Week 12 / Full Analysis Set
Table 14.2-2.5.3	Change from Baseline in Partial Mayo Clinic Score at Week 12 / Full Analysis Set

Number	Title
Table 14.2-3.1.1	Summary of Score and Change from Baseline in MMES During Long-Term Extension Therapy Period / Full Analysis Set
Table 14.2-3.1.2	Summary of Score and Change from Baseline in MMES During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-3.2.1	Summary of Score and Change from Baseline in UCEIS During Long-Term Extension Therapy Period / Full Analysis Set
Table 14.2-3.2.2	Summary of Score and Change from Baseline in UCEIS During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-3.3.1	Summary of Score and Change from Baseline in Total Mayo Score During Long-Term Extension Period / Full Analysis Set
Table 14.2-3.3.2	Summary of Score and Change from Baseline in Total Mayo Score During Open-Label Extension Period / Full Analysis Set
Table 14.2-3.3.3	Summary of Score and Change from Baseline in Partial Mayo Clinic Scores During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.3.4	Summary of Score and Change from Baseline in Partial Mayo Clinic Scores During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.1	Summary Score and Change from Baseline in IBDQ Total Score During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.2	Summary Score and Change from Baseline in IBDQ Total Score During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.3	Summary Score and Change from Baseline in IBDQ - Bowel-Related Symptoms Score During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.4	Summary Score and Change from Baseline in IBDQ - Bowel-Related Symptoms Score During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.5	Summary Score and Change from Baseline in IBDQ - Systemic Function Score During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.6	Summary Score and Change from Baseline in IBDQ - Systemic Function Score During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.7	Summary Score and Change from Baseline in IBDQ - Social Function Score During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.8	Summary Score and Change from Baseline in IBDQ - Social Function Score During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set

Number	Title
Table 14.2-3.4.9	Summary Score and Change from Baseline in IBDQ - Emotional Status Score During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.4.10	Summary Score and Change from Baseline in IBDQ - Emotional Status Score During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.5.1	Summary Score and Change from Baseline in Corticosteroid (Glucocorticoid) Dosages During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.5.2	Summary Score and Change from Baseline in Corticosteroid (Glucocorticoid) Dosages During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.5.3	Summary Score and Change from Baseline in Duration of Corticosteroid-Free Treatment During Long-Term Extension Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.5.4	Summary Score and Change from Baseline in Duration of Corticosteroid-Free Treatment During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.6	Percentage of Clinical Response at Week 52 During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.7	Percentage of Clinical Response at Week 52 During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-3.8.1	Change from Baseline in UCEIS at Week 52 During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.8.2	Change from Baseline in Total Mayo Clinic Score at Week 52 During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.8.3	Change from Baseline in Total Partial Clinic Score at Week 52 During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.8.4	Mean Change from Baseline in Partial Mayo Clinic Scores During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Mixed Model for Repeated Measures / Full Analysis Set
Table 14.2-3.9.1	Summary of Score and Change from Baseline in Mayo Clinic Score - Stool Frequency During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.9.2	Summary of Score and Change from Baseline in Mayo Clinic Score - Stool Frequency During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.9.3	Summary of Score and Change from Baseline in Mayo Clinic Score - Rectal Bleeding During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.9.4	Summary of Score and Change from Baseline in Mayo Clinic Score - Rectal Bleeding During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.9.5	Summary of Score and Change from Baseline in Mayo Clinic Score - Physician's Global Assessment During Double-

Number	Title
	Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.9.6	Summary of Score and Change from Baseline in Mayo Clinic Score - Physician's Global Assessment During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.2-3.9.7	Summary of Score and Change from Baseline in Modified Baron Endoscopic Score During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.9.8	Summary of Score and Change from Baseline in Modified Baron Endoscopic Score During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-3.9.9	Summary of Score and Change from Baseline in UCEIS Subscore - Vascular Pattern During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.9.10	Summary of Score and Change from Baseline in UCEIS Subscore - Vascular Pattern During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-3.9.11	Summary of Score and Change from Baseline in UCEIS Subscore - Bleeding During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.9.12	Summary of Score and Change from Baseline in UCEIS Subscore - Bleeding During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-3.9.13	Summary of Score and Change from Baseline in UCEIS Subscore - Erosions and Ulcers During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-3.9.14	Summary of Score and Change from Baseline in UCEIS Subscore - Erosions and Ulcers During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-8.1	Summary of Score and Change from Baseline in MMES During Double-Blind Therapy / Full Analysis Set
Table 14.2-8.2	Summary of Score and Change from Baseline in MMES During Open-Label Extension Therapy / Full Analysis Set
Table 14.2-8.3	Summary of Score and Change from Baseline in UCEIS During Double-Blind Therapy / Full Analysis Set
Table 14.2-8.4	Summary of Score and Change from Baseline in UCEIS During Open-Label Extension Therapy Period / Full Analysis Set
Table 14.2-8.5	Summary of Score and Change from Baseline in Total Mayo Score During Double-Blind Therapy Period / Full Analysis Set
Table 14.2-8.6	Summary of Score and Change from Baseline in Total Mayo Score During Open-Label Extension Period / Full Analysis Set
Table 14.2-8.7	Summary of Score and Change from Baseline in Partial Mayo Score During Double-Blind Therapy Period and Double-

Number	Title
	Blind Therapy Follow-Up Period / Full Analysis Set
Table 14.2-8.8	Summary of Score and Change from Baseline in Partial Mayo Score During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Table 14.3.1-1.1	Overall Summary of Treatment-Emergent Adverse Events During Study / Safety Analysis Set
Table 14.3.1-1.2	Summary of Treatment-Emergent Adverse Events During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-1.3	Summary of Treatment-Emergent Adverse Events During Double-Blind Induction Therapy Period / Safety Analysis Set
Table 14.3.1-1.4	Summary of Treatment-Emergent Adverse Events During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-2.1	Treatment-Emergent Adverse Events By System Organ Class and Preferred Term During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-2.2	Treatment-Emergent Adverse Events By System Organ Class and Preferred Term Double-Blind Induction Therapy Period / Safety Analysis Set
Table 14.3.1-2.3	Treatment-Emergent Adverse Events By System Organ Class and Preferred Term During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-2.4	Treatment-Emergent Adverse Events By System Organ Class, Preferred Term and Relationship to Investigational Product During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-2.5	Treatment-Emergent Adverse Events By System Organ Class, Preferred Term and Relationship to Investigational Product During Double-Blind Induction Therapy Period / Safety Analysis Set
Table 14.3.1-2.6	Treatment-Emergent Adverse Events By System Organ Class, Preferred Term and Relationship to Investigational Product During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-3.1	Treatment-Emergent Adverse Events By Maximum Severity, System Organ Class and Preferred Term During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-3.2	Treatment-Emergent Adverse Events By Maximum Severity, System Organ Class and Preferred Term During Double-Blind Induction Therapy Period / Safety Analysis Set
Table 14.3.1-3.3	Treatment-Emergent Adverse Events By Maximum Severity, System Organ Class and Preferred Term During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-4.1	Serious Treatment-Emergent Adverse Events By System Organ Class and Preferred Term During Double-Blind Therapy

Number	Title
	Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-4.2	Serious Treatment-Emergent Adverse Events By System Organ Class and Preferred Term During Double-Blind Induction Therapy Period / Safety Analysis Set
Table 14.3.1-4.3	Serious Treatment-Emergent Adverse Events By System Organ Class and Preferred Term During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-5.1	Treatment-Emergent Adverse Events Leading to Discontinuation from The Study By System Organ Class and Preferred Term During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.1-5.2	Treatment-Emergent Adverse Events Leading to Discontinuation from The Study By System Organ Class and Preferred Term During Double-Blind Induction Therapy Period / Safety Analysis Set
Table 14.3.1-5.3	Treatment-Emergent Adverse Events Leading to Discontinuation from The Study By System Organ Class and Preferred Term During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-1.1	Vital Signs and Body Weight and Change from Baseline During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-1.2	Vital Signs and Body Weight and Change from Baseline During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.1	Summary of Clinical Laboratory Values-Hematology During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.2	Summary of Clinical Laboratory Values-Hematology During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.3	Summary of Clinical Laboratory Values- Serum Chemistry During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.4	Summary of Clinical Laboratory Values- Serum Chemistry During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.5	Summary of Clinical Laboratory Values- Coagulation Profile During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.6	Summary of Clinical Laboratory Values- Coagulation Profile During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set

Number	Title
Table 14.3.4-2.7	Summary of Clinical Laboratory Values- Urinalyses During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.8	Summary of Clinical Laboratory Values- Urinalyses During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.9	Shift Table of Clinical Laboratory Values -Hematology During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.10	Shift Table of Clinical Laboratory Values -Hematology During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.11	Shift Table of Clinical Laboratory Values - Serum Chemistry During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.12	Shift Table of Clinical Laboratory Values - Serum Chemistry During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.13	Shift Table of Clinical Laboratory Values -Coagulation Profile During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.14	Shift Table of Clinical Laboratory Values -Coagulation Profile During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.15	Shift Table of Clinical Laboratory Values - Urinalyses During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-2.16	Shift Table of Clinical Laboratory Values - Urinalyses During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.1	12-Lead Electrocardiogram Parameters During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.2	12-Lead Electrocardiogram Parameters During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.3	12-Lead Electrocardiogram: Summary of Elevated QTCF Values During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.4	12-Lead Electrocardiogram: Summary of Elevated QTCF Values During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set

Number	Title
Table 14.3.4-3.5	12-Lead Electrocardiogram: QTCF Change from Baseline - Categorical Analysis During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.6	12-Lead Electrocardiogram: QTCF Change from Baseline - Categorical Analysis During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.7	12-Lead Electrocardiogram: QTCF Categorical Analysis During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.8	12-Lead Electrocardiogram: QTCF Categorical Analysis During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.9	12-Lead Electrocardiogram: Shift Table of QTCF Values During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Table 14.3.4-3.10	12-Lead Electrocardiogram: Shift Table of QTCF Values Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set

9.4.1 Tables for Un-Blinded 12 Week Induction Therapy Data

Number	Title
Table 14.1.1	Disposition of Subjects for Induction Therapy Period
Table 14.1.4.1	Demographics (Safety Analysis Set)
Table 14.2.1.1	Baseline and Change from Baseline of Modified Mayo Endoscopic Score (MMES) at Week 12 (induction Therapy)
Table 14.2.1.2	Analysis of Change from Baseline in MMES at Week 12
Table 14.2.2.1	Baseline and Change from Baseline in UCEIS at Week 12
Table 14.2.2.2	Baseline and Change from Baseline in Total Mayo Clinic Score at Week 12
Table 14.2.2.3	Partial Mayo Clinic Score during Induction Therapy
Table 14.2.2.4	Clinical Improvement (%) at Week 12 in MMES, Modified Baron Endoscopic Score, Mucosal Healing, Clinical Response and Clinical Remission
Table 14.2.2.5.1	Analysis of Change from Baseline in UCEIS at Week 12
Table 14.2.2.5.2	Analysis of Change from Baseline in Total Mayo Clinic Score at Week 12
Table 14.2.2.5.3	Analysis of Change from Baseline in Partial Mayo Clinic Score at Week 12

Number	Title
Table 14.2.3.9.1	Baseline and Change from Baseline in Mayo Clinic Score - Stool Frequency during 12 Week Induction Therapy
Table 14.2.3.9.3	Baseline and Change from Baseline in Mayo Clinic Score - Rectal Bleeding during 12 Week Induction Therapy
Table 14.2.3.9.7	Baseline and Change from Baseline in Modified Baron Endoscopic Score at 12 Week Induction Therapy
Table 14.2.3.9.9	Baseline and Change from Baseline in UCEIS Subscore - Vascular Pattern at 12 Week Induction Therapy
Table 14.2.3.9.11	Baseline and Change from Baseline in UCEIS Subscore - Bleeding at 12 Week Induction Therapy
Table 14.2.3.9.13	Baseline and Change from Baseline in UCEIS Subscore - Erosions and Ulcers at 12 Week Induction Therapy
Table 14.3.1.1.3	Overall Summary of Treatment Emergent Adverse Events during Induction Therapy
Table 14.3.1-2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term during Double-Blind Induction Therapy Period
Table 14.3.1.2.5	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term during Double Blind Induction Therapy.
Table 14.3.1.4.2	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term during Double-Blind Induction Therapy Period

9.5 Figures

Number	Title
Figure 15.1.1	Least Squares Means Adjusted for Baseline of MMES at Week 12 / Full Analysis Set
Figure 15.1.2	Difference in Least Squares Means from Placebo Adjusted for Baseline of MMES at Week 12 / Full Analysis Set
Figure 15.2.1	Least Squares Means of UCEIS at Week 12 / Full Analysis Set
Figure 15.2.2	Difference in Least Squares Means from Placebo of UCEIS at Week 12 / Full Analysis Set
Figure 15.2.3	Least Squares Means of Total Mayo Clinic Scores at Week 12 / Full Analysis Set
Figure 15.2.4	Difference in Least Squares Means from Placebo of Total Mayo Clinic Scores at Week 12 / Full Analysis Set
Figure 15.2.5	Least Squares Means of Partial Mayo Clinic Scores at Week 12 / Full Analysis Set
Figure 15.2.6	Difference in Least Squares Means from Placebo of Partial Mayo Clinic Scores at Week 12 / Full Analysis Set
Figure 15.3.1	MMES During Double-Blind Therapy Period / Full Analysis Set
Figure 15.3.2	MMES During Open-Label Extension Therapy Period / Full Analysis Set

Number	Title
Figure 15.3.3	UCEIS During Double-Blind Therapy Period / Full Analysis Set
Figure 15.3.4	UCEIS During Open-Label Extension Therapy Period / Full Analysis Set
Figure 15.3.5	Total Mayo Clinic Scores During Double-Blind Therapy Period / Full Analysis Set
Figure 15.3.6	Total Mayo Clinic Scores During Open-Label Extension Therapy Period / Full Analysis Set
Figure 15.3.7	Partial Mayo Clinic Scores During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Full Analysis Set
Figure 15.3.8	Partial Mayo Clinic Scores During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Figure 15.3.9	Change from Baseline of MMES During Double-Blind Therapy Period / Full Analysis Set
Figure 15.3.10	Change from Baseline of MMES During Open-Label Extension Therapy Period / Full Analysis Set
Figure 15.3.11	Change from Baseline of UCEIS During Double-Blind Therapy Period / Full Analysis Set
Figure 15.3.12	Change from Baseline of UCEIS During Open-Label Extension Therapy Period / Full Analysis Set
Figure 15.3.13	Change from Baseline of Total Mayo Clinic Scores During Double-Blind Therapy Period / Full Analysis Set
Figure 15.3.14	Change from Baseline of Total Mayo Clinic During Open-Label Extension Therapy Period / Full Analysis Set
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Figure 15.3.16	Change from Baseline of Partial Mayo Clinic Scores During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Full Analysis Set
Figure 15.4.1	Laboratory-Hematology During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.4.2	Laboratory-Hematology During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.4.3	Laboratory-Clinical Chemistry During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.4.4	Laboratory-Clinical Chemistry During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.4.5	Laboratory- Coagulation Profile During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set

Number	Title
Figure 15.4.6	Laboratory- Coagulation Profile During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.4.9	12-Lead Electrocardiogram Parameters During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.4.10	12-Lead Electrocardiogram Parameters During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.1	Change from Baseline of Laboratory-Hematology During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.2	Change from Baseline of Laboratory-Hematology During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.3	Change from Baseline of Laboratory-Clinical Chemistry During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.4	Change from Baseline of Laboratory-Clinical Chemistry During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.5	Change from Baseline of Laboratory- Coagulation Profile During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.6	Change from Baseline of Laboratory- Coagulation Profile During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.7	Change from Baseline of 12-Lead Electrocardiogram Parameters Profile During Double-Blind Therapy Period and Double-Blind Therapy Follow-Up Period / Safety Analysis Set
Figure 15.5.8	Change from Baseline of 12-Lead Electrocardiogram Parameters During Open-Label Extension Therapy Period and Open-Label Extension Therapy Follow-Up Period / Safety Analysis Set

9.6 Listings

Number	Title
Listing 16.2.1-1.1	Disposition of Subjects - / All Subjects
Listing 16.2.1-1.2	Screening Failures / Screening Failure Subjects
Listing 16.2.2-1	Protocol Deviations / Randomized Subjects
Listing 16.2.2-2	Violations of Inclusion / Exclusion Criteria / Randomized Subjects
Listing 16.2.3-1	Populations for Analysis / Randomized Subjects
Listing 16.2.4-1	Demographics and Baseline Characteristic / Randomized Subjects
Listing 16.2.4-2	Baseline UC Assessment and UC Diagnosis / Randomized Subjects
Listing 16.2.4-3	Pregnancy Test / Randomized Subjects
Listing 16.2.4-4	Medical / Surgical History / Randomized Subjects
Listing 16.2.4-5	Physical Examinations / Randomized Subjects
Listing 16.2.5-1	Prior and Concomitant Medications / Randomized Subjects
Listing 16.2.5-2	Study Medication Administration / Randomized Subjects
Listing 16.2.5-3	Study Medication Duration and Number of Dose / Randomized Subjects
Listing 16.2.6-1	MMES at All Study Visits / Randomized Subjects
Listing 16.2.6-2.1	UCEIS and Baron Endoscopic Score at All Study Visits / Randomized Subjects
Listing 16.2.6-2.2	Total and Partial Mayo Clinic Scores at All Study Visits / Randomized Subjects
Listing 16.2.6-2.3	Clinical Response at Week 12 and Week 52 / Randomized Subjects
Listing 16.2.6-3.1	Total and 4 Subscale IBDQ Scores at All Study Visits / Randomized Subjects
Listing 16.2.6-3.2	Corticosteroid Dosages and The Duration of Glucocorticoid-Free Treatment / Randomized Subjects
Listing 16.2.7-1	Pre-Treatment Adverse Events / Summary of All Subjects / Randomized Subjects
Listing 16.2.7-2.1	Treatment-Emergent Adverse Events / Randomized Subjects
Listing 16.2.7-2.2	Serious Treatment-Emergent Adverse Events / Randomized Subjects
Listing 16.2.7-2.3	Treatment-Emergent Adverse Events Leading to Deaths / Randomized Subjects
Listing 16.2.7-2.4	Treatment-Emergent Adverse Events Leading to Discontinuation / Randomized Subjects
Listing 16.2.7-2.5	Treatment-Emergent Adverse Events with Withdrawal of Investigational Product / Randomized Subjects

Number	Title
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Listing 16.2.8-2	Clinical Laboratory Values-Hematology / Randomized Subjects
Listing 16.2.8-3	Clinical Laboratory Values-Clinical Chemistry / Randomized Subjects
Listing 16.2.8-4	Clinical Laboratory Values- Coagulation Profile / Randomized Subjects
Listing 16.2.8-5	Clinical Laboratory Values-Urinalysis / Randomized Subjects
Listing 16.2.8-6	Clinical Abnormal Laboratory Values / Randomized Subjects
Listing 16.2.8-7	12-Lead Ecg - Quantitative Data / Randomized Subjects

9.7 Table, Figure, and Listing shells

Table, figure, and listing shells are provided in a separate document.

10. Literature and references

- *CROS NT Standard Operating Procedure ST/03_V01 "Statistical Analysis Plan";*
- *European Medicines Agency (EMA), International Conference on Harmonisation (ICH) E3 Harmonised Guideline (1996) "Structure and Content of Clinical Study Reports";*
- *EMA, ICH E9 Harmonised Guideline (1998) "Statistical Principles for Clinical Trials".*