

## CLINICAL PROTOCOL

**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**

### REVISED TO INCORPORATE AMENDMENT 2

**Protocol Number:** 4083-002

**Original Protocol:** 14AUG2015

**Amendment 1** 15OCT2015

**Amendment 2** 04OCT2016

**Phase:** 2

**US IND Number:** 124049

**EudraCT Number:** 2015-001555-69

**Sponsor:** Kyowa Kirin Pharmaceutical Development, Inc.  
212 Carnegie Center, Suite 101  
Princeton, NJ 08540 USA

#### Confidentiality Statement

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## Principal Investigator Signature Page

**Protocol Title:** 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

**Protocol Number:** 4083-002, Amendment 2

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Any supplemental information (e.g., protocol amendment, Investigator's Brochure, and study manuals) that may accompany this document are also proprietary to KKD and should be handled consistent with the terms stated above.

I, the undersigned, have reviewed this protocol, including appendices. I will conduct the clinical study in compliance with the protocol, study manuals, good clinical practice (GCP), and the applicable regulatory requirements.

### Principal Investigator:

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Institution

\_\_\_\_\_  
Address

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## Protocol Signature Page

**Protocol Title:** 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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**Signature**

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**Date**

## Summary of Changes

### REASON FOR THE AMENDMENT:

The changes that were made to the protocol are listed in the following table, along with the rationale for each change:

Section	Change	Rationale
Section 5 OBJECTIVES	Revised objectives to include the open-label extension.	Revised in accordance with changes in the study design.
Section 6.1 Overall Study Design and Plan	The study plan was revised to: 1) Convert the post induction phase of the study from a blinded long-term extension to an open-label extension. 2) Add investigative sites in the Czech Republic.	1) The protocol was amended to allow all eligible subjects to receive KHK4083 after the 12-week, double-blind induction phase. Subjects currently enrolled in the long-term extension who are receiving study medication but who are non-responders up to the Week 28 visit will be eligible to receive KHK4083 in the open-label study extension. 2) Sites in the Czech Republic will be added to the study to ensure complete accrual.
Section 6.1.3 Open-label Extension Therapy: Week 12 (First Dose) to Week 52	Section added	Revised in accordance with changes in the study design.
Section 6.1.4 Transitioning from the Long-term Extension to the Open-label Extension	Section added	Revised in accordance with changes in the study design.
Section 6.3 Study Safety Monitoring Plan	1) The Safety Monitoring Committee will evaluate the cumulative safety data available after the first 4 subjects in a cohort at Week 6 for the 3.0 and 10 mg/kg dose cohorts instead of Week 8. 2) The Safety Monitoring Committee and Sponsor may dose-reduce cohorts or not escalate to the planned doses based upon review of safety data. 3) The dose administered during the open-label extension will be the same as the dose for that cohort during the induction therapy,	1) KHK4083 concentrations in serum at Week 6 are estimated to be approximately 10% lower than those at Week 8 based on the elimination half-life of the drug. This small difference in drug exposure at Week 6 and Week 8 is not expected to affect the detection of safety signals and will allow for an earlier review of the safety data. 2) To clarify how dose reductions for a cohort will occur. 3) To clarify how the dose for the open-label extension will be selected.

Section	Change	Rationale
	unless dose-reduction is recommended by the Safety Monitoring Committee and Sponsor.	
Section 7.3 Exclusion Criterion 2)	Subjects with well-controlled immunologic, autoimmune or chronic inflammatory disorders, other than ulcerative colitis, or autoimmune connective tissue diseases may be included, after consulting with the medical monitor.	Ulcerative colitis is often accompanied by involvement of organs besides the colon and/or other autoimmune or chronic inflammatory diseases. Including subjects with stable, well-controlled disease outside of the colon will result in inclusion of a more representative population of subjects with ulcerative colitis.
Section 7.3 Exclusion Criterion 3)	The definition of biologic treatment history has been revised from “failed to respond to more than one biologic treatment” to “failed to respond to two or more biologic treatments with different mechanism of action”	Clarification of criteria. Note that some patients with moderate ulcerative colitis receive two or more anti-TNF monoclonal antibodies, and failure to respond to drugs with similar mechanisms of action is not felt to impact the assessment of efficacy or safety.
Section 7.3 Exclusion Criterion 4)	Modified to allow subjects receiving stable doses of oral budesonide $\leq 9$ mg/day to participate.	Amended to harmonize this criterion with Inclusion Criterion #6
Section 7.3 Exclusion Criterion 23) (see also Section 7.1 Procedures for Enrollment)	A subject who was considered a screen failure and not dosed with investigational product is permitted to be re-screened once due to failure to meet the Inclusion/Exclusion Criteria, whereas subjects with other reasons for lack of randomization may be re-screened twice.	To allow for re-screening in cases where a subject fails screening because all assessments were not completed within the 28-day screening window
Section 7.4 Additional Criteria to Enroll in Open-label Extension Therapy	Criteria to participate in the long-term extension have been replaced with criteria to enroll in the open-label extension	Revised in accordance with changes in the study design.

Section	Change	Rationale
Section 7.5.3 Criteria for Subject Removal from Treatment and the Study	A subject who has two consecutive visits during Induction Therapy with a worsening from Baseline, in partial Mayo Clinic score of $\geq 3$ points (e.g., partial Mayo Clinic score of 3 at baseline, 6 at Week 2, and 6 at Week 4) or two consecutive visits during maintenance therapy with a worsening from Week 12 in partial Mayo Clinic score of $\geq 3$ points at a visit and $\geq 5$ points at the next visit may continue to receive study medication if the Investigator, with agreement from the Sponsor, determines that there has not been clinically significant worsening.	As the patient-reported stool frequency and bloodiness for the Partial Mayo clinical score is the average of the last 2 to 3 days prior to a visit, the diaries may not always reflect the subject's and physician's perception of the UC disease activity. This permits an additional dose of study medication to be administered on a case-by-case basis for subjects who may not have clinically significant worsening.
Section 7.5.4 End-of-Treatment Visit	Section added. Assessments have been amended as follows: If the subject discontinues during Induction Therapy, a sigmoidoscopy will be performed at End-of-Treatment/Week 12 if the subject discontinues more than 8 weeks after Baseline visit; the sigmoidoscopy may be performed up to 4 weeks after the last dose of study medication. If the subject discontinues during OLE/LTE therapy, a sigmoidoscopy will be performed at End-of-Treatment/Week 52 if the subject discontinues more than 8 weeks after the Week 12 visit; the sigmoidoscopy may be performed up to 8 weeks after the last dose of study medication.	The section was added to clarify the End-of-Treatment procedures. The timing of the End-of-Treatment sigmoidoscopy for subjects who discontinue prematurely was changed, as the primary analysis for endoscopic findings is at 12 weeks after administration of 5 of 6 doses of study medication. This clarifies when a sigmoidoscopy should occur and which timeframe is considered too short for the purposes of this study for an End-of-treatment sigmoidoscopy.

<b>Section</b>	<b>Change</b>	<b>Rationale</b>
7.5.5 End-of-Study Visit	Section added	The section was added to clarify the End-of-Study procedures.
Section 8.1.2 Investigational Product Destruction	Removed the mandate for destruction of investigational product at the site.	Sites participating in the study that have been unable to destroy the investigational product on site have contacted the Sponsor and alternate destruction arrangements have been made.
Section 8.1.3.4 Dose Modifications	Clarified that dose reduction is not permitted for an individual subject. Doses chosen for each cohort, as determined by the Safety Monitoring Committee and Sponsor, may result in dose reduction for all subjects enrolled in a cohort.	In order to determine the safety profile for KHK4083, individual subjects are not permitted to dose reduce. Dose reduction for a cohort may occur based upon evaluation of safety by the Safety Monitoring Committee and Sponsor.
Section 9.1 Screening Period (Day -28 to Day -1)	For subjects who are rescreened, the original screening sigmoidoscopy can be used to satisfy the entry criteria if obtained within 42 days prior to the first dose.	To obviate the need for a second sigmoidoscopy during re-screening, if performed up to 42 days prior to Day 1.
Section 10.4.1 Pharmacokinetic and Pharmacodynamic Assessments	The visit schedule for Part A has been revised to eliminate study visits on Days 3 and 4 in Weeks 0, 10, and 48. The pharmacokinetic timepoints on Day 3 and Day 4 in Week 0, Week 10 and Week 48 were removed. The PD timepoint was moved from Day 4 to Day 2 because of elimination of the Day 4 visit.	Considering the characteristics of the PK profile for KHK4083 following intravenous administration, the PK sampling timepoints on Day 3 and Day 4 are deemed not critical in determination of the PK disposition of KHK4083. The revised PK sampling schedule is considered adequate to assess the PK of KHK4083 in this study. The PD timepoint is moving from Day 4 to Day 2 to coincide with the change in the visit schedule.
Appendix 6 Follow-up and End-of-Study for Subjects who Discontinued During the Study	Added study diagram	To clarify the End-of-Study and Follow-up visits

Additional revisions include updating the company name from Kyowa Hakko Kirin Pharma, Inc. to Kyowa Kirin Pharmaceutical Development, Inc. (a.k.a. the Sponsor or KKD throughout the document) and the list of Adverse Event Contacts.

Cross-referencing has been used to represent the changes listed above and edits have been made in all sections of the protocol, as applicable.

## Adverse Event Contacts

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# 1 SYNOPSIS

<b>Name of Sponsor/Company:</b> Kyowa Kirin Pharmaceutical Development, Inc.	<b>Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:</b>  <b>Volume:</b>  <b>Reference:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> KHK4083		
<b>Name of Active Ingredient:</b> KHK4083		
<b>Title of Study:</b> 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		
<b>Protocol Number:</b> 4083-002, Amendment 2		
<b>Investigators and Study Center(s):</b> Multicenter at approximately 40 investigative sites in the United States (US), Russia, Hungary, Poland, Romania, Serbia and Czech Republic; other countries may be included as needed.		
<b>Phase of Development:</b> Phase 2		
<b>Objectives:</b> <b>Primary:</b> <ul style="list-style-type: none"> <li>• 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 ulcerative colitis (UC) to recommend for use in Part B;</li> <li>• 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).</li> </ul> <b>Secondary:</b> <ul style="list-style-type: none"> <li>• To determine if KHK4083 at dose levels different than the recommended dose improve the mucosa based on the mMES;</li> <li>• To determine if any dose level of KHK4083 administered as Induction Therapy will meet the following objectives at Week 12 (or as noted):                             <ul style="list-style-type: none"> <li>– Improve the mucosa based on the modified Baron endoscopic score;</li> <li>– Improve the mucosa based on the Ulcerative Colitis Endoscopic Index of Severity (UCEIS);</li> <li>– Induce mucosal healing based on the mMES;</li> <li>– Improve clinical signs and symptoms based on total Mayo Clinic score;</li> <li>– Improve clinical signs and symptoms based on partial Mayo Clinic scores (Week 2 through Week 12, excludes endoscopy subscores);</li> <li>– 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);</li> <li>– Induce clinical remission based on a total Mayo Clinic score (i.e., score of <math>\leq 2</math>) and subscores (i.e., no subscores <math>&gt; 1</math>).</li> </ul> </li> <li>• To characterize the pharmacokinetics (PK) of KHK4083 in subjects with moderately active UC following multiple dose administration;</li> </ul>		

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<ul style="list-style-type: none"> <li>• To evaluate the development of antibodies against KHK4083 (immunogenicity).</li> </ul> <p><b>Exploratory:</b></p> <ul style="list-style-type: none"> <li>• 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:                     <ul style="list-style-type: none"> <li>– Improve clinical signs and symptoms based on total Mayo Clinic score;</li> <li>– 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);</li> <li>– 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);</li> <li>– Induce clinical remission based on a total Mayo Clinic score and subscores;</li> <li>– Induce durable clinical responses and durable clinical remissions (present at both Weeks 12 and 52), and glucocorticoid-free clinical remission;</li> <li>– Induce mucosal healing based on the mMES;</li> <li>– Improve the mucosa based on the mMES, UCEIS, and/or modified Baron endoscopic score;</li> <li>– 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).</li> </ul> </li> <li>• To evaluate the activity of KHK4083 on health-related quality of life, which will be based on the subject’s completed Inflammatory Bowel Disease Questionnaires (IBDQs) in comparison with Baseline assessments;</li> <li>• To measure changes from Baseline in corticosteroid (glucocorticoid) dosages;</li> <li>• To determine the percentage of subjects who are glucocorticoid-free from Week 16 through Week 52, and the OLE/LTE Therapy Follow-up Period (Week 56 through Week 64);</li> <li>• To evaluate the pharmacodynamic (PD) profile of KHK4083;</li> <li>• To explore the PK-PD relationships.</li> </ul>		
<p><b>Study Design:</b></p> <p>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, long-term extension (LTE) under preceding versions of the protocol who worsen may be eligible to transition to the OLE up to Week 28. Selected Sponsor personnel will be unblinded after the last subject completes Induction Therapy. Post-treatment assessments will continue for 16 weeks after the last infusion associated with the subject’s treatment period. The doses selected for this study are based on a Phase 1a/1b single-ascending dose study, which showed that KHK4083 was well tolerated and there were no dose-limiting adverse effects up to 10 mg/kg, the highest dose studied.</p>		

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<p><b>Screening Period (Day –28 to Day –1):</b>                  At the Screening visit, the Investigator will review the written informed consent form (ICF) with each subject to ensure that the subject understands the study and the study procedures. The subject will read, sign, and date the ICF and other locally applicable documents. Screening evaluations used to determine the subject’s study eligibility must be completed within the Screening Period (Day –28 to Day –1) prior to starting treatment on Day 1 (Week 0), and include a baseline sigmoidoscopy with biopsy being completed within 7 to 28 days prior to Day 1. For subjects who are rescreened, the original screening sigmoidoscopy can be used to satisfy the entry criteria if obtained within 42 days prior to Day 1. All sigmoidoscopy procedures will be performed using a flexible sigmoidoscope.</p> <p><b>Double-blind Treatment Period (Weeks 0 to 12/52):</b>                  Each subject must be carefully monitored at the investigative site for signs of acute, potential dose-limiting toxicity infusion reactions during and for at least 3 hours following the completion of the first and second intravenous (IV) infusions of investigational product, and for at least 1 hour following all other IV infusions. In addition, a phone call to each subject will be conducted at approximately 48 to 72 hours following the completion of the first and second infusions for any subject who does not return for a visit at the investigative site.</p> <p><b>Induction Therapy: Week 0 to Week 12 (Last Dose at Week 10)</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 each cohort will be randomly assigned in a 3:1 ratio to receive KHK4083 or placebo by IV infusion over 60 minutes (<math>\pm</math> 10 minutes).</p> <p><b>Induction Therapy - Part A:</b>                  In the first 3 cohorts, 27 subjects (9 subjects/cohort) will receive KHK4083 and 9 subjects (3 subjects/cohort) will receive placebo once every 2 weeks (Weeks 0 to 10) as follows:                      Cohort 1: 1.0 mg/kg or placebo                      Cohort 2: 3.0 mg/kg or placebo                      Cohort 3: 10 mg/kg or placebo</p> <p>The cumulative safety data available after the first 8 of 12 subjects randomized in Cohort 1 will be evaluated by the Safety Monitoring Committee at Week 4 (~Day 29) to assess whether dosing will continue for subjects within Cohort 1 and if investigational product will be administered at the next higher dose level for subjects in Cohort 2. For Cohorts 2 and 3, the cumulative safety data available after the first 8 subjects in each cohort at Week 4 (~Day 29) with the first 4 subjects in each cohort at Week 6 (~Day 43) will be evaluated for continuation of all of the subjects and for dose escalation in the next cohort, i.e., Cohort 3 in Part A and Cohort 4 in Part B, respectively. The Safety Monitoring Committee and Sponsor may dose-reduce cohorts or not escalate to the planned doses based upon review of safety data.</p>		

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<p><b><u>Induction Therapy - Part B:</u></b></p> <p>The recommended dose (one of three dose levels in Cohorts 1 - 3 selected based on the safety data from Part A) will be administered once every 2 weeks (Weeks 0 to 10) to additional subjects (18 subjects to receive KHK4083, 6 subjects to receive placebo) in Cohort 4 who did not participate in Part A.</p> <p>For subjects in all cohorts, a sigmoidoscopy with biopsy is scheduled at Week 12 to assess improvement in the mucosa from Baseline (Week 0) to Week 12. It is highly recommended that the sigmoidoscopy with biopsy be performed within 7 to 13 days prior to the Week 12 visit.</p> <p><b>Long-term Extension Therapy: Week 12 (First Dose) to Week 52</b></p> <p>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.</p> <p>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. 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. Mucosal healing is defined as a mMES of 0 or 1.</p> <p>All subjects who qualified were to have been given two options:</p> <ol style="list-style-type: none"> <li>1) To receive no further treatment and proceed directly to the Induction Therapy Follow-up Period (Week 16 through Week 26); or</li> <li>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).</li> </ol> <p>Note: Subjects who already started treatments in the double-blind LTE therapy will continue to receive KHK4083 or placebo during LTE Therapy. If their UC worsens or flares up to the Week 28 visit, they may transition to the OLE</p> <p>Subjects who did not qualify were to have received no further treatment and entered the Induction Therapy Follow-up Period.</p> <p>Subjects in the double-blind LTE may enter the OLE up to the Week 28 visit if their UC worsens or flares.</p> <p><b>Open-label Extension Therapy: Week 12 (First Dose) to Week 52</b></p> <p>Subjects who complete double-blind Induction Therapy (i.e., at least five of six treatments) are eligible to continue in open-label treatment OLE Therapy (refer to Section 7.4 for specific eligibility criteria).</p>		

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<p>All subjects who qualify will be given two options:</p> <ol style="list-style-type: none"> <li>1) To receive no further treatment and proceed directly to the Induction Therapy Follow-up Period (Week 16 through Week 26); or</li> <li>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).</li> </ol> <p>Subjects who do not qualify will receive no further treatment and will enter the Induction Therapy Follow-up Period.</p> <p>Each subject must be carefully monitored at the investigative site for signs of acute, potential dose-limiting toxicity infusion reactions during and for at least 3 hours following the completion of the first and second intravenous (IV) infusions of the open-label, investigational product, and for at least 1 hour following all other IV infusions. In addition, a phone call to each subject will be conducted at approximately 48 to 72 hours following the completion of the first and second infusions for any subject who does not return for a visit at the investigative site.</p> <p><b>End-of-Treatment Visit</b></p> <p>An End-of-Treatment visit must be conducted for all subjects who discontinue from treatment. This visit must occur within 2 weeks or 4 weeks after the last dose of investigational product of Induction Therapy or OLE/LTE Therapy, respectively. If the subject discontinues during Induction Therapy, a sigmoidoscopy will be performed at End-of-Treatment/Week 12 if the subject discontinues more than 8 weeks after Baseline visit; the sigmoidoscopy may be performed up to 4 weeks after the last dose of study medication.</p> <p>If the subject discontinues during OLE/LTE therapy, a sigmoidoscopy will be performed at End-of-Treatment/Week 52 if the subject discontinues more than 8 weeks after the Week 12 visit; the sigmoidoscopy may be performed up to 8 weeks after the last dose of study medication.</p> <p><b>End-of-Study Visit</b></p> <p>If the subject is withdrawn from the study, and thus no subsequent visits are planned, then the Investigator must complete all applicable final visit procedures.</p> <p><b>Post-treatment Follow-up Period:</b></p> <p>Three on-site follow-up visits for post-treatment assessments will be conducted 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. Subjects removed from the study for adverse events (AEs) will be followed until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved.</p> <p><b>Primary Endpoints:</b></p> <p>Subjects with moderately active UC will primarily be evaluated for an improvement in the mucosa determined by</p>		

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<b>Name of Active Ingredient:</b> KHK4083		
<p>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.</p> <p>The safety and tolerability of KHK4083 will be determined by physical examination, vital signs, body weight, 12-lead electrocardiograms (ECGs), and clinical laboratory findings; and the number and percentage of subjects reporting AEs, serious adverse events (SAEs), and treatment discontinuation due to AEs.</p>		
<p><b>Selection of Subjects:</b></p> <p>Subjects may be included in the study if they meet all of the following <u>Inclusion Criteria</u>:</p> <ol style="list-style-type: none"> <li>1) Subject is able and willing to comply with study procedures, and to adhere to dosing and visit schedules and follow-up procedures as described in the protocol and ICF;</li> <li>2) Subject voluntarily signs/dates an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF in accordance with regulatory and institutional guidelines; <i>Note: Written informed consent must be obtained prior to performing any study-related procedure.</i></li> <li>3) Male and female subjects <math>\geq</math> 18 years of age at the time of enrollment;</li> <li>4) Subject has UC that was diagnosed at least 6 months prior to the Screening visit;</li> <li>5) Subject has moderately active UC, defined as:             <ol style="list-style-type: none"> <li>a) Total Mayo Clinic score of 4 to 9 (range: 0 to 12, with higher scores indicating more disease activity);</li> <li>b) Endoscopy subscore (mMES determined by a central reader) of at least 2; and</li> <li>c) Disease that extends <math>\geq</math> 15 cm from the anal verge.</li> </ol> </li> <li>6) Subject has had previous treatment (within 5 years prior to Screening) with one or more of the following: corticosteroids, immunosuppressive medications, or tumor necrosis factor (TNF) antagonist therapy that was unsuccessful because of a lack of efficacy response or AEs, as defined below:             <ol style="list-style-type: none"> <li>a) corticosteroids for induction therapy of at least prednisolone-equivalent of 20 mg (or oral budesonide 9 mg) oral daily for 2 weeks or injectable for 1 week, or for maintenance therapy at least two failed attempts to reduce to less than prednisolone-equivalent 10 mg (or oral budesonide 3 mg) oral daily, or a history of intolerance to corticosteroids (including but not limited to hypertension, insomnia, osteopenia, osteoporosis, hyperglycemia, infection or Cushing's syndrome);</li> <li>b) Azathioprine or 6-mercaptopurine of at least 1.5 mg/kg/day or 0.75 mg/kg/day, respectively, for 8 weeks, or a history of intolerance to either agent (including but not limited to nausea, vomiting, abdominal pain, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations, thiopurine methyltransferase genetic mutation, or infection);</li> <li>c) tumor necrosis factor-alpha antagonists for induction therapy with approved anti-TNF products including, but not limited to, infliximab 5 mg/kg IV for 2 doses at least 2 weeks apart, adalimumab 160 mg SC followed by at least 80 mg SC at least 2 weeks apart, and golimumab</li> </ol> </li> </ol>		

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<p>200 mg SC followed by at least 100 mg at least 2 weeks apart and anti-TNF biosimilar products with approved dosages for 2 doses at least 2 weeks apart; or as maintenance therapy for recurrence of symptoms despite continued dosing, or history of intolerance (including but not limited to infusion or injection reactions, demyelination or infection).</p> <p>7) Female subjects who are considered to be women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening and Baseline. WOCBP must agree to use effective contraception, defined as oral contraceptives with one barrier method, or tubal ligation with one barrier method or double barrier method (condom plus spermicide or diaphragm plus spermicide) during the study and for at least 6 months after the last dose of investigational product. Subjects are considered to not be of childbearing potential if they are <math>\geq 50</math> years of age and without menses for 24 consecutive months and have a follicle-stimulating hormone level <math>&gt; 25</math> mIU/mL (or in postmenopausal range per local laboratory standards); or have undergone a hysterectomy and/or a bilateral salpingo-oophorectomy. Egg donation is not permitted while on study medication and for at least 6 months after the last dose of study medication.</p> <p>8) Male subjects (including those who have had a vasectomy) must use adequate contraception (e.g., latex condom, non-latex condom not made of natural animal membrane such as polyurethane condom) during the study and for at least 6 months after the last dose of investigational product. Sperm donation is not permitted while on study medication and for at least 6 months after the last dose of study medication.</p> <p>Subjects must be excluded from participating in this study if they meet any of the following <u>Exclusion Criteria</u>:</p> <ol style="list-style-type: none"> <li>1) Subject, who, for any reason, is judged by the Investigator to be inappropriate for this study, including a subject who is unable to communicate or cooperate with the Investigator, who has/had a psychiatric illness, disability or social situation that may compromise the safety of the subject during the study or affect the ability of the subject to adhere to study procedures;</li> <li>2) Subject has a medical history of clinically significant (as determined by the Investigator or the Sponsor) cardiac, renal, hepatic/biliary (e.g., sclerosing cholangitis), pulmonary, or other medical conditions or is not generally in good health. Subjects with the history of immunologic, autoimmune or chronic inflammatory disorders (e.g., uveitis, rheumatoid arthritis, ankylosing spondylitis or spondyloarthritis, psoriasis) other than UC or autoimmune connective tissue diseases (e.g., systemic lupus erythematosus, systemic sclerosis) and are well controlled may be included into the trial after consultancy with medical monitor. Subjects with thyroid disorders, vitiligo, or alopecia are eligible for inclusion.</li> <li>3) Subject's UC had failed to respond to:                         <ol style="list-style-type: none"> <li>a) Two or more biologic treatments with different mechanisms of action (e.g., infliximab and vedolizumab), or</li> <li>b) Three or more anti-TNF biologics (e.g. infliximab, adalimumab, and golimumab).</li> </ol> </li> <li>4) Subject requires prescription treatment for UC, except for the stable, oral treatment of UC, as follows:                         <ol style="list-style-type: none"> <li>a) Aminosalicylates (5-aminosalicylic acid [5-ASA] or mesalamine <math>\leq 4.8</math> g/day; sulfasalazine</li> </ol> </li> </ol>		

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<p>≤ 3 g/day) for at least 14 days prior to the Screening visit; and/or</p> <ul style="list-style-type: none"> <li>b) Glucocorticoids (≤ 20 mg/day prednisolone or the equivalent, or budesonide ≤ 9 mg/day) for at least 14 days prior to the Screening visit (or for 4 weeks if a course of corticosteroids had started at less than 8 weeks prior to Screening visit); and/or</li> <li>c) Azathioprine up to 3 mg/kg/day or 6-mercaptopurine up to 1.5 mg/kg/day for a total treatment period of at least 12 weeks, including 4 weeks of stable treatment, prior to the Screening visit.</li> </ul> <p>5) Subject has received any of the following prior treatments or treatments within the specified time:</p> <ul style="list-style-type: none"> <li>a) Natalizumab, efalizumab or rituximab or other lymphocyte-depleting treatments, including but not limited, to alkylating agents (such as cyclophosphamide or chlorambucil) and total lymphoid irradiation at any time prior to randomization (Baseline visit);</li> <li>b) TNF antagonists within 8 weeks, or 5 half-lives (based on maximum duration but not exceeding 12 weeks), prior to randomization (Baseline visit);</li> <li>c) Vedolizumab within 16 weeks prior to randomization (Baseline visit);</li> <li>d) Methotrexate, cyclosporine, mycophenolate, tacrolimus, thalidomide, or other immune altering drugs within 4 weeks prior to randomization (Baseline visit) (ophthalmologic preparations are permitted);</li> <li>e) 5-ASA enema, or steroid enema or suppository use within 2 weeks prior to randomization (Baseline visit); and/or</li> <li>f) Investigational agents within 8 weeks or 5 half-lives (if pharmacology information is available) prior to randomization (Baseline visit), whichever is longer.</li> </ul> <p>6) Subject with recent (within 1 year prior to Screening), suspected or confirmed symptomatic stenosis of the colon, abdominal abscess, or ischemic colitis based on clinical or radiographic data; or who has suspected, confirmed or a history of toxic megacolon; or with any colonic resection, subtotal or total colectomy, ileostomy, or colostomy; or who had any previous surgery for UC or an anticipated requirement for surgery for UC;</p> <p>7) Subject with known colonic dysplasia, adenomas or polyposis;</p> <p>8) Subject had major surgery within 4 weeks prior to Screening or an anticipated requirement for major surgery;</p> <p>9) Subject with enteric pathogens (including Clostridium difficile) detected on stool analysis; or Clostridium difficile infection within 8 weeks prior to Screening; or intestinal pathogen infection detected within 4 weeks prior to Screening;</p> <p>10) Subject with any of the following hematological and chemistry laboratory values:</p> <ul style="list-style-type: none"> <li>a) Platelet count &lt; 100,000/mm<sup>3</sup>;</li> <li>b) Neutrophils &lt; 1500/mm<sup>3</sup>;</li> <li>c) Serum creatinine ≥ 1.6 mg/dL (≥ 144.4 μmol/L);</li> <li>d) Alkaline phosphatase &gt; 3 times the upper limit of normal (ULN);</li> <li>e) Aspartate aminotransferase or ALT &gt; 2 times ULN;</li> <li>f) Total bilirubin &gt; 2 mg/dL, unless due to Gilbert’s Syndrome;</li> </ul>		

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<p>g) Serum albumin &lt; 3 g/dL;</p> <p>h) Hemoglobin &lt; 9 g/dL;</p> <p>i) Glycated serum hemoglobin A1c ≥ 9%.</p> <p>11) Subject has a clinically significant cardiac disease (class II, III, or IV of the New York Heart Association classification) (The Criteria Committee of the New York Heart Association Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 1994); unstable angina pectoris; myocardial infarction within 6 months or is post angioplasty or stenting within 6 months; uncontrolled hypertension; or clinically significant abnormality, such as cardiac arrhythmia, on a 12-lead ECG at Screening;</p> <p>12) Subject is pregnant or breastfeeding;</p> <p>13) Subject has had a major immunologic reaction (e.g., serum sickness, anaphylaxis, or anaphylactoid reaction);</p> <p>14) Subject is Hepatitis B core antibody or surface antigen positive at Screening and/or Hepatitis C antibody positive with detectable RNA at Screening;</p> <p>15) Subject has a history of human immunodeficiency virus (HIV) positivity, tests positive for HIV at Screening, or has congenital or acquired immunodeficiency;</p> <p>16) Subject has or has had active tuberculosis (TB), suspected extra-pulmonary TB, a history of incompletely treated TB, or latent TB or other latent infection. Subjects with latent TB (purified protein derivative [PPD] or interferon gamma release assay [IGRA]) may be included in the study if prophylactic therapy for latent TB is started at least 4 weeks prior to Screening. Subjects with a potentially untreated other infection (clinical findings) are to be excluded.  <i>Note: Performing of both IGRA and PPD tests in the same subject should be avoided as screening procedures. Positivity of one of the tests cannot be voided by negativity of the other, i.e., subjects with positive PPD and negative IGRA test performed as a part of Screening will be considered TB positive and will be required to start prophylactic anti-TB therapy prior to infusion of investigational product according to local treatment standards. All safety laboratory tests may be repeated. Screening procedures may be extended by 2 weeks.</i></p> <p>17) Subject has bacterial infections requiring treatment with oral or parenteral antibiotics (topical antibiotics are allowed), within 2 and 4 weeks, respectively, of the Screening period;</p> <p>18) Subject has a history of systemic opportunistic infection or recurrent infections;</p> <p>19) Subject has malignancy or history of malignancy, except for adequately treated basal cell skin cancer or adequately treated carcinoma in-situ of the cervix without recurrence, and treatment must have been completed at least 5 years before the Screening Period;</p> <p>20) Subject who received a bacille Calmette-Guérin (BCG) vaccine within 6 months of randomization or live vaccination (e.g., measles, mumps, rubella [MMR]; herpes zoster; varicella; intranasal influenza; and oral poliomyelitis) within 4 weeks of randomization is to be excluded. Subject is allowed vaccinations of inactivated vaccines (e.g., hepatitis, pneumococcal, meningococcal, tetanus, diphtheria toxoid, acellular pertussis, inactivated polio, human papilloma and influenza – except intranasal influenza);</p> <p>21) Subject with a history of substance abuse within 1 year of Screening; or active marijuana</p>		

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(medicinal or recreational) use or active substance abuse; 22) Subject has other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results, as determined by the Investigator; 23) Subject who previously participated in a study of KHK4083. <i>Note: A subject who was considered a Screen failure and not dosed with investigational product in the current study (4083-002) is permitted to be re-screened once due to failure to meet the Inclusion/Exclusion Criteria, whereas subjects with other reasons for lack of randomization may be re-screened twice.</i>		
<b>Additional Criteria to Enroll in OLE Therapy:</b> Prior to receiving one infusion every 4 weeks of KHK4083 in the OLE, subjects must meet the following criteria: <ol style="list-style-type: none"> <li>1) Subjects must have completed double-blind Induction Therapy, i.e., at least five of six double-blind treatments, or the subject is already in the double-blind LTE and not beyond Week 28 with a clinical worsening or a flare of disease as defined by the Investigator);</li> <li>2) Subjects must have evaluable total Mayo Clinic scores at baseline and Week 12;</li> <li>3) Subjects must have been compliant with the protocol (including concomitant medication restrictions); and</li> <li>4) Subjects may have no clinically significant additional risks, as determined by the Investigator or the Sponsor, of treatment with KHK4083.</li> </ol>		

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<b>Number of Subjects Planned:</b> 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.		
<b>Treatment of Subjects:</b>		
<b>Duration of Treatment:</b> A total of up to 52 weeks of double-blind treatment includes 12 weeks of Induction Therapy (Part A and Part B) and 40 weeks of OLE/LTE Therapy.		
<b>Induction Therapy (12 weeks):</b>		
<ul style="list-style-type: none"> <li>• Part A (Cohorts 1 - 3): Each subject will be administered one IV infusion of KHK4083 or placebo once every 2 weeks for a total of 6 treatments, i.e., on Day 1 (Week 0), Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), and Day 71 (Week 10).</li> <li>• Part B (Cohort 4): Each subject will be administered an IV infusion of the recommended KHK4083 dose selected in Part A (one of three dose levels in Cohorts 1 - 3) or placebo once every 2 weeks for a total of 6 treatments.</li> </ul>		
<b>Investigational Product:</b>		
<ul style="list-style-type: none"> <li>• Part A (Cohorts 1 - 3): KHK4083 1.0 mg/kg (Cohort 1); 3.0 mg/kg (Cohort 2); and 10 mg/kg (Cohort 3).</li> <li>• Part B (Cohort 4): KHK4083 recommended dose (one of three dose levels in Cohorts 1 - 3).</li> </ul>		
<b>Control (Cohorts 1 - 4):</b> Placebo IV infusion as treatment during Induction Therapy.		
<b>Open-label / Long-term Extension Maintenance Therapy: Week 12 (First Dose) to Week 52</b>		
All subjects who qualify and continue double-blind LTE or start open-label maintenance therapy will be administered one KHK4083 or placebo (LTE) or one KHK4083 (OLE) IV infusion at Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 for a total of 10 additional treatments. Some subjects in the LTE may transition to the OLE after Week 12 and up to Week 28. The treatment at Week 12 will be administered at the scheduled visit or within 7 days after Week 12.		
<b>Efficacy, Pharmacokinetics, Pharmacodynamics, Immunogenicity, and Safety Variables</b>		
<b>Efficacy:</b>		
The efficacy variables include mMES, UCEIS score, modified Baron endoscopic score, total Mayo Clinic score, partial Mayo Clinic score (without sigmoidoscopy), and an IBDQ score.		
<b>Pharmacokinetics:</b>		
The PK variables include maximum observed serum concentration ( $C_{max}$ ), time of maximum observed serum concentration ( $t_{max}$ ), trough concentration at the end of the dosing interval ( $C_{min}$ ), area under the serum concentration-time curve ( $AUC_{0-t}$ , $AUC_{0-\tau}$ , $AUC_{0-\infty}$ ), terminal elimination half-life ( $t_{1/2}$ ), systemic serum clearance (CLs), volume of distribution at steady state ( $V_{ss}$ ), volume of distribution at terminal phase ( $V_z$ ), and accumulation ratio ( $R_{ac}$ ).		
<b>Pharmacodynamics:</b>		
The PD variables include the measurement of fecal calprotectin and C-reactive protein (using wr-CRP assay) concentrations. Other PD assessments include delayed-type hypersensitivity skin testing with the <i>Candida</i>		

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<p><i>albicans</i> antigen (at all investigative sites in the US and in other selected countries), immunohistochemical staining on all endoscopic biopsy samples, and flow cytometry analyses on whole blood or peripheral blood mononuclear cells for the measurement of specific immune-related cells.</p> <p><b>Immunogenicity:</b>                  For immunogenicity, the development of anti-KHK4083 antibodies will be assessed.</p> <p><b>Safety:</b>                  The safety variables include AEs (including SAEs), physical examinations, vital signs, body weight, 12-lead ECGs, and clinical laboratory evaluations (serum chemistry, hematology, coagulation profile, multiplex-31 assays, and urinalysis).</p>		
<p><b>Safety Management and Monitoring:</b>                  Kyowa Kirin Pharmaceutical Development, Inc. has primary responsibility for the ongoing medical review of safety data throughout the study.</p> <p>Recommendations will be made with the input of the Medical Monitor to the Principal Investigator and other appropriate designated staff regarding further conduct of the study. The Safety Monitoring Committee will evaluate the cumulative safety data available after the first 8 subjects (1.0 mg/kg dose cohort) at Week 4. For subsequent dose escalation, the Safety Monitoring Committee will evaluate the cumulative safety data available and after the first 8 subjects in a cohort at Week 4 and with the first 4 subjects in a cohort at Week 6 for the 3.0 and 10 mg/kg dose cohorts. At each of the timepoints, the committee will assess whether dosing will continue for all subjects and if the investigational product will be administered at the next higher dose level for subjects in the next cohort in Part A or for Cohort 4 in Part B. A separate Safety Monitoring Committee Charter will identify the membership and define the specific procedures of the committee.</p>		
<p><b>Statistical Methods and Planned Analysis:</b>                  All categorical variables will be summarized by counts and percentages. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for continuous variables will be utilized. All summaries and analyses conducted will be by treatment cohort (KHK4083 dose levels; combined KHK4083; and placebo) and by visit. The last pre-administration observation will be used as the Baseline value for calculating post-administration changes from Baseline. All data obtained on the electronic case report form and entered into the database will be provided in separate data listings showing individual subject values.</p> <p>The following analysis sets will be used in the study:</p> <p><b>Safety Analysis Set:</b> Includes all subjects who received any investigational product (even a partial dose);</p> <p><b>Full Analysis Set:</b> 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.</p> <p>Treatment-emergent adverse events (TEAEs) will be grouped and tabulated by the <i>Medical Dictionary for Regulatory Activities Preferred Term</i> and System Organ Class. 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., Induction</p>		

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<p>Therapy and LTE or OLE Therapy) and by cohort (KHK4083 versus placebo) during Induction Therapy, OLE or LTE Therapy.</p> <p>The overall safety and tolerability of KHK4083 compared to placebo administered in multiple IV doses will be determined for all safety variables.</p> <p>All efficacy analyses will be performed in the FAS unless otherwise specified. All statistical analyses in this Phase 2 study will be descriptive or exploratory, and no adjustment to control Type I error will be performed.</p> <p><b>Pharmacokinetic, Pharmacodynamic, and Immunogenicity Methods:</b></p> <p>The PK parameters (i.e., <math>C_{max}</math>, <math>t_{max}</math>, <math>C_{min}</math>, <math>AUC_{0-t}</math>, <math>AUC_{0-\infty}</math>, <math>t_{1/2}</math>, CLs, <math>V_{ss}</math>, <math>V_z</math>, and <math>R_{ac}</math>) for KHK4083 will be summarized by dose level and Treatment Period. The dose proportionality of KHK4083 PK exposure parameters will be assessed using the Power Model for Cohorts 1 - 3 (Induction Therapy - Part A and LTE Therapy). The PK exposure parameters include <math>C_{max}</math>, <math>AUC_{0-t}</math>, and <math>AUC_{0-\infty}</math>, as appropriate.</p> <p>The PD parameters will be determined and summarized by dose level and Treatment Period. The PK-PD relationships will be explored using graphic tools or modeling as needed.</p> <p>The immunogenicity of KHK4083 will be determined and the percentage of subjects with confirmed anti-KHK4083 antibodies will be summarized by dose level and Treatment Period, visit (week), and overall. The effect of positive anti-KHK4083 antibodies on the PK, and possibly efficacy and safety, will be explored.</p> <p>Serum samples, which will be collected at specified times throughout the study, will be assessed using multiplex-31 assays at four sample collection timepoints: Baseline (Week 0), Week 2, Week 12 (End-of-Induction Therapy), and Week 52 (End-of-OLE/LTE Therapy) or at a follow-up visit if the subject does not continue in OLE/LTE Therapy. For other potential study assessments (e.g., exploratory biomarker analyses), whole blood samples will be collected and stored (frozen) for future analysis.</p>			

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### 3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

#### Abbreviations

AE	adverse event
ALT	alanine aminotransferase
APC	antigen-presenting cell
ASA	aminosalicylic acid
AST	aspartate aminotransferase
BCG	bacille Calmette-Guérin
CD	cluster of differentiation
CFR	Code of Federal Regulations
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGRA	interferon gamma release assay
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KKD	Kyowa Kirin Pharmaceutical Development, Inc.
LTE	long-term extension
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mMES	modified Mayo endoscopy subscore
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	purified protein derivative

### Abbreviations (continued)

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TNF- $\alpha$	tumor necrosis factor-alpha
TNFR	tumor necrosis factor receptor
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential
wr-CRP	wide-range C-reactive protein

### Definitions (Refer to Appendix 1 for Primary and Secondary Efficacy Definitions)

AUC	area under the concentration-time curve
AUC <sub>0-t</sub>	area under the serum drug concentration-time curve from 0 to the last measurable concentration
AUC <sub>2wk</sub>	area under the serum drug concentration-time curve at 2 weeks post-dose
AUC <sub>0-<math>\tau</math></sub>	area under the serum drug concentration-time curve within a dosing interval
AUC <sub>0-<math>\infty</math></sub>	area under the serum drug concentration-time curve from 0 to infinity
CLs	systemic serum clearance
C <sub>max</sub>	maximum observed serum concentration
C <sub>min</sub>	trough concentration at the end of the dosing interval
%CV	percent coefficient of variation
R <sub>ac</sub>	accumulation ratio
SD	standard deviation
t <sub>1/2</sub>	terminal elimination half-life
t <sub>max</sub>	time of maximum observed serum concentration
V <sub>ss</sub>	volume of distribution at steady state
V <sub>z</sub>	volume of distribution at terminal phase

## **4 BACKGROUND INFORMATION**

### **4.1 Ulcerative Colitis**

Inflammatory bowel diseases (IBDs) comprise ulcerative colitis (UC) and Crohn's disease, which are considered to be common gastrointestinal autoimmune diseases, and are referred to as immune-mediated inflammatory diseases. (Mahmood, 2012; Khor, 2011) A peak incidence of UC occurs early in adult life (15 to 30 years) with a greater prevalence in males, nonsmokers or ex-smokers, and in developed countries. (Loftus, 2004; Hanauer, 2006) The global incidence rate of UC varies greatly from 0.5 to 24.5 per 100,000 persons. (Lakatos, 2006)

Urbanization and variances in exposure to sunlight, pollution, and industrial chemicals are considered potential contributing factors to IBD. (Hanauer, 2006) Other factors such as diet, oral contraceptives, perinatal and childhood infections, or atypical mycobacterial infections have been suggested but not proven to play a role. (Loftus, 2004)

Ulcerative colitis symptoms include abdominal pain/cramps, diarrhea that is usually bloody, and severe urgency to have a bowel movement. The symptoms can be intermittent with fairly long periods between flare-ups and remission. Fatigue and loss of appetite with subsequent weight loss are common. Complications can include severe abdominal bloating, bleeding from deep ulcerations, anemia, fulminant colitis, and toxic megacolon potentially leading to perforation of the colon. In addition, there may be skin lesions, joint pain, eye inflammation, and liver disorders. Patients with UC are at increased risk of colon cancer. (Centers for Disease Control and Prevention, IBD, 2015)

Ulcerative colitis is characterized by inflammation limited to the colon that begins in the rectum and affects the superficial layers of the colon in an even and continuous distribution. The inflammatory changes are limited to the mucosa and submucosa with cryptitis and crypt abscesses. Ulcerative colitis is considered to result from an improper mechanism and continuing inflammatory response to commensal microbes and environmental conditions in patients with genetic risk factors. (Khor, 2011) The intestinal mucosa exists in a functional equilibrium with the complex luminal environment dominated by a spectrum of microbial species and their products. A functional balance is essential to maintaining normal mucosal physiology. In addition to nutrient absorption, intestinal epithelial cells perform both barrier and signal-transduction functions. Patients often have a compromised mucosa and an increase in presence of mucolytic bacteria. (Khor, 2011)

Genome-wide association studies have identified 99 non-overlapping genetic risk loci in IBD including 47 risk loci specific to UC of which approximately 30% (28) of IBD-related genetic loci are shared between UC and Crohn's disease. (Franke, 2010; Anderson, 2011) Analyses of the genes and genetic loci that contribute to IBD susceptibility show a multitude of pathways that are critical for intestinal homeostasis, including barrier function, epithelial restitution, microbial defense, innate immune regulation, reactive oxygen species generation, autophagy, regulation of adaptive immunity, endoplasmic reticulum stress, and metabolic pathways associated with cellular homeostasis. Homeostasis in the gut involves a balance between anti-inflammatory and pro-inflammatory signals, whereas an inadequate T-reg-cell response occurs with a heightened response mainly involving Th2 cells in UC. (Khor, 2011)

A recent study showed significantly enhanced apoptosis of circulating lymphocytes in IBD patients during flare-ups compared to remission and is considered to be possibly a consequence of the systemic disease process. (El-Hodhod, 2013) Increased circulating lymphocytes apoptosis may also be attributed to a deficiency in nutrients, which is common in IBD patients. (Bager, 2011; El-Hodhod, 2013; Nakajima, 2011; Levin, 2011; O'Malley, 2011; Yakut, 2010)

Cells with high synthetic capacity and secretory activity (e.g., Paneth and goblet) have high baseline levels of endoplasmic reticulum stress, leading to activation of the unfolded protein response, which controls cellular programs that allow proper protein processing. This response is mainly cytoprotective, although it can signal apoptosis after sustained endoplasmic reticulum stress. (Khor, 2011) The role of apoptosis in intestinal lymphocytes in IBD shows that the inflamed gut T-cells have a resistance to apoptosis, a prolonged survival, and an increased cytokine production that may significantly aggravate the inflammation, whereas noninflamed gut T-cells have an increased susceptibility towards apoptosis that limits expansion of T-cells and down regulates mucosal immune responses. (Sturm, 2008)

In addition to its effects on cell viability and disruption of normal intestinal homeostasis, due to an imbalance of production and apoptosis, sustained endoplasmic reticulum stress also activates autophagy and IL-23 release, and may engage inflammatory circuits that are subsequently propagated by T cells. (Goodall, 2010; Kaser, 2008; Khor, 2011)

Apoptotic cells have been shown to actively suppress inflammatory responses by reducing the lifespan of activated lymphocytes. (Bodar, 2007; El-Hodhod, 2013; Fadok, 2001) Thus, apoptosis plays a critical role in lymphocyte development and homeostasis. Enhanced lymphocyte apoptosis can cause immunodeficiency through cell loss. Conversely, inhibition of apoptosis can lead to the development of autoimmunity or lymphoma. Two major

pathways contribute to the regulation of lymphocyte cell death, death by neglect and death by instruction. (El-Hodhod, 2013; Rathmell, 2002) Increased circulating lymphocyte apoptosis could also be considered as a protective mechanism against organ injury as increased lymphocyte apoptosis was found to be linked to anti-inflammatory cytokine secretion and thereby may contribute to preventing unwanted immune response and organ injury. (El-Hodhod, 2013; Neuman, 2007)

The event that initiates the immune response in IBD has not been identified, but possible factors include a pathogenic and nonpathogenic organism, an immune response to an intraluminal antigen (e.g., protein from cow milk), or an autoimmune process. (Abraham, 2011; El-Hodhod, 2013; Nell, 2010) During an immune response, homeostasis is disturbed as antigen-presenting cells (APCs) become activated and promote the clonal expansion of antigen-specific lymphocytes. Shortly after the peak of the response, controlled induction of apoptosis, of both APCs and lymphocytes, restores homeostasis. This process is critical to ensure protective immunity and avoid lymphoid neoplasia and autoimmunity. (El-Hodhod, 2013; Hildeman, 2007) The influence of tumor necrosis factor (TNF) on the function of APCs varies as TNF can either activate APCs, augment antigen presentation capability, or upregulate the expression of costimulatory molecules, or TNF can inhibit the function of mature lymphocytes and possibly induce their apoptosis and impair antigen presentation to prevent the organ damage. It has been demonstrated that the addition of apoptotic lymphocytes to endotoxin-stimulated peripheral blood mononuclear cells (PBMCs) causes a shift from secretion of proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-12) to anti-inflammatory cytokines (IL-10). (Voll, 1997)

#### **4.2 Current Treatment of Ulcerative Colitis and Associated Benefit/Risks**

Topical or oral 5-aminosalicylic acid (5-ASA) is the first line of treatment for mild to moderately active UC. Patients with persistently active disease are then typically given oral glucocorticoids to induce remission. Once remission is achieved, maintenance therapy, typically with 5-ASA, is recommended for those with left-sided colitis, pancolitis or extensive disease.

Patients with severe UC are usually treated with oral glucocorticoids, high dose oral 5-ASA and topical therapy, and often receive antibiotic treatment as well as nutritional support. Patients with severe or corticosteroid-dependent disease receive additional treatment, such as azathioprine or 6-mercaptopurine, or a biologic agent. Tumor necrosis factor-alpha (TNF- $\alpha$ ) blockers are used to treat autoimmune diseases, including Crohn's disease and UC, either

after first-line immunosuppressors (e.g., azathioprine or 6-mercaptopurine) or in association with these treatments. (Silva, 2010)

The following are approved TNF- $\alpha$  blockers:

- Chimeric IgG monoclonal antibody (mAb) infliximab (Remicade; Inflectra and Remsima - in the European Union [EU] only) - UC/Crohn's disease
- Human IgG mAb adalimumab (Humira) - UC/Crohn's disease
- Fully human mAb golimumab (Simponi) - UC
- Pegylated humanized Fab' fragment certolizumab pegol (Cimzia) - Crohn's disease in the United States (US) only

A humanized IgG1 mAb, vedolizumab (Entyvio<sup>®</sup>), which is an integrin receptor antagonist (i.e., binds to the human  $\alpha 4\beta 7$  integrin) is approved for both UC and Crohn's disease in the US and EU.

Serious and sometimes fatal adverse effects have been reported with TNF- $\alpha$  blockers (Silva, 2010), including infections due to bacterial, mycobacterial (e.g., tuberculosis [TB]), invasive fungal infections (e.g., histoplasmosis, aspergillosis, candidiasis, coccidiomycosis, blastomycosis, and pneumocystosis), viral (e.g., hepatitis B), or other opportunistic pathogens (e.g., *Listeria* and *Legionella*). (US Food and Drug Administration, Drug Safety Communications, 2011 and 2013) Lymphoma, including a rare and fatal type called hepatosplenic T-cell lymphoma, and other malignancies, can occur in adults and children. Other serious risks include melanoma and Merkel cell carcinoma, heart failure, demyelinating disorders, hypersensitivity reactions, and hepatitis B reactivation. (Marion, 2013)

A review of the subject's prior medical history of neoplasias and infections, and evaluation for active TB and demyelinating diseases, testing for hepatitis B viral infection and latent infection should be conducted. (Silva, 2010)

### **4.3 KHK4083 - Investigational Product**

#### **4.3.1 KHK4083 Development**

KHK4083 is a fully human, non-fucosylated IgG1 mAb specific for the costimulatory molecule OX40 (cluster of differentiation [CD]134, tumor necrosis factor receptor [TNFR]SF4), a 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. OX40 has a unique pattern of expression, being restricted to antigen-activated,

effector T-cells (mostly CD4<sup>+</sup>), transient, and present in diseased areas in human autoimmune diseases.

OX40 has been shown to be highly expressed in the gastrointestinal tissue of patients with autoimmune diseases of the gastrointestinal tract (e.g., celiac, UC, Crohn's disease). In a study on the expression of OX40, all UC and Crohn's disease and most celiac disease biopsy tissue samples (formalin-fixed, paraffin-embedded tissue stained with anti-OX40 antibody and alkaline phosphatase-anti alkaline phosphatase method [APAAP]) were positive, indicating the potential role of OX40 in pathogenesis of these diseases. (Stüber, 2000)

Expression of lymphocyte-endothelial receptor-ligand pairs,  $\alpha 4\beta 7$ /MAdCAM-1 and OX40/OX40 ligand in the colon and jejunum of patients with IBD also have been assessed by using endoscopic and per oral jejunal biopsy specimens that were immunostained (i.e., by indirect alkaline phosphatase using antibodies against CD3, ICAM-1,  $\alpha 4\beta 7$ , MAdCAM-1, and OX40). The expression of MAdCAM-1 and OX40 ligand on gut endothelial and OX40<sup>+</sup> cells was increased in sites of mucosal inflammation in patients with IBD. There was no evidence of increased lamina propria T-cells or increased vascular adhesion molecule expression in the proximal intestine of patients with distal IBD. (Souza, 1999)

### 4.3.2 Nonclinical Development

The generation of the KHK4083 mAb and its *in vitro* characterization as well as the non-clinical pharmacology, pharmacokinetics (PK), and toxicology study reports are thoroughly described in the Investigator's Brochure. All nonclinical safety studies were conducted in Japan, a member country of the Organisation for Economic Co-operation and Development (OECD) and compliant with the Mutual Acceptance of Data program. The studies conducted in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) are identified in the Investigator's Brochure. The nonclinical/toxicological program includes a pivotal 4-week intravenous (IV) GLP study (SBL303-081) and a pivotal 26-week subcutaneous (SC) and IV GLP study (SBL303-104) in cynomolgus monkeys. In these studies, the no-observed-adverse-effect levels (NOAELs) were  $\geq 100$  mg/kg (IV) and  $\geq 30$  mg/kg (both SC and IV), in 4-week IV and 26-week SC and IV study, respectively. The mean  $AUC_{0-\infty}$  (area under the serum drug concentration-time curve from 0 to infinity) and mean  $C_{max}$  for male and female monkeys in the 100 mg/kg dose group were 607000  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 5345  $\mu\text{g}/\text{mL}$ , respectively, after the first dose. The mean  $AUC_{0-2\text{wk}}$  (area under the serum drug concentration-time curve from 0 to 2 weeks post-dose) and mean  $C_{max}$  for male and female monkeys in the 30 mg/kg IV group were 301500  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 1510  $\mu\text{g}/\text{mL}$ , respectively, after the 13th dose (i.e., steady state). The

AUCs were used to calculate the safety margins for the dose levels planned for this Phase 2 study. Refer to Section 8.1.3.1 for additional details on safety margins and selection of doses.

### **4.3.3 Clinical Program**

The clinical program comprises a Phase 1a/1b study (4083-001, completed in December 2014) in subjects with mild to moderate plaque-type psoriasis at 4 clinical sites in Canada. KHK4083 was well-tolerated and no dose-limiting toxicity was identified in the Phase 1a/1b, single-ascending dose study of up to 10 mg/kg, the highest dose studied.

The implementation of this study is based on the premise that KHK4083 may have the potential to reduce OX40-bearing lymphocytes, which have been reported in colonic biopsies of patients with UC. (Stüber, 2000) In sites of mucosal inflammation, the expression of OX40 ligand on gut endothelial and OX40+ cells was increased in the colon and jejunum of patients with IBD. (Souza, 1999) Thus, further study of KHK4083 is planned for IBD, in particular in subjects with UC.

## **5 OBJECTIVES**

The primary, secondary (including PK and immunogenicity), and exploratory objectives of the study (refer to Appendix 1 for primary and secondary efficacy definitions) are as follows:

### **Primary:**

- **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).

The assessment is based on a mean change in the 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. Refer to Mayo Clinic Scoring System for Assessment of Ulcerative Colitis Activity (Score 0 to 12) with Modified Mayo Endoscopy Subscore Appendix 2 for the mMES Scoring System.

### **Secondary:**

- 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 (or as noted):

- Improve the mucosa based on the modified Baron endoscopic score; Refer to Appendix 3 for the modified Baron scoring system.
  - Improve the mucosa based on the Ulcerative Colitis Endoscopic Index of Severity (UCEIS);  
The assessment is based on 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. Refer to Appendix 4 for the UCEIS Scoring System.
  - 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  $\leq 2$ ) 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).
- Refer to Section 10.2 for additional details on all secondary endpoints.

**Exploratory:**

- To determine if multiple doses of KHK4083 administered during the Open-label Extension (OLE) / Long-term Extension (LTE) Therapy phase 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 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 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.

Refer to Section 10.3 for additional details on exploratory endpoints.

## **6 STUDY DESIGN**

### **6.1 Overall Study Design and Plan**

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 design was revised to convert the post induction phase of the study from a LTE to an OLE.

Male and female subjects  $\geq 18$  years of age with moderately active UC, defined as a total Mayo Clinic score of 4 to 9 (range: 0 - 12, with higher scores indicating more active disease) with an mMES of at least 2 as determined by a central reader, and disease that extends  $\geq 15$  cm from the anal verge are eligible to participate in this study.

This multicenter study will be conducted at approximately 40 investigative sites in the US, Russia, Hungary, Poland, Romania, Serbia, and Czech Republic; other countries may be included as needed. 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.

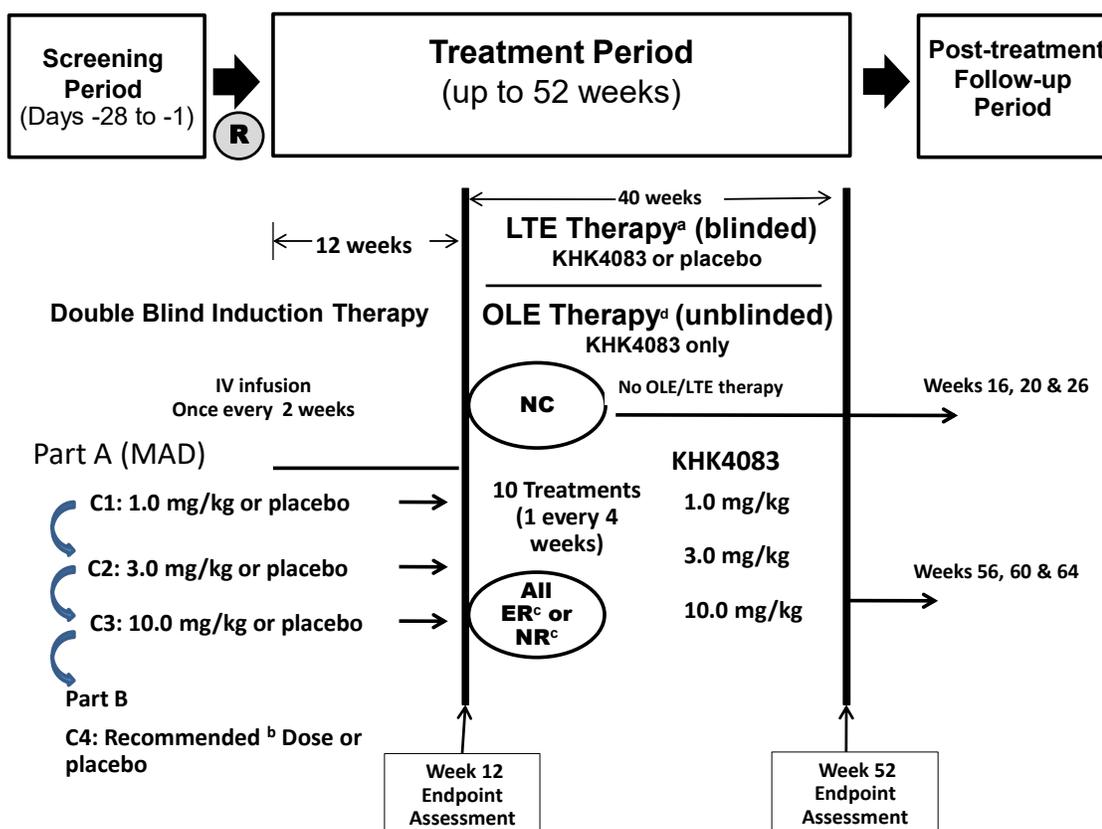
The Treatment Period includes double-blind Induction Therapy (12 weeks) and OLE Therapy (40 weeks) for eligible subjects at Week 12. Subjects already enrolled in the double-blind, LTE under preceding versions of the protocol who worsen may be eligible to transition to the OLE up to Week 28. Selected Kyowa Kirin Pharmaceutical Development, Inc. (hereinafter

referred to as the Sponsor) personnel will be unblinded after the last subject completes Induction Therapy (refer to Section 8.4 for details).

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.

The Study design is displayed in Figure 6.1-1.

**Figure 6.1-1 Study Design Diagram**



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.

### **6.1.1 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.

Subjects in each cohort will be randomly assigned in a 3:1 ratio to receive KHK4083 or placebo by IV infusion over 60 minutes ( $\pm$  10 minutes). Each subject will receive a total of 6 treatments (one IV infusion per treatment) every 2 weeks from Week 0 (Day 1) to Week 10 of Induction Therapy. Safety assessments (e.g., after 2 treatments for 1.0 mg/kg and 3 treatments for 3.0 and 10 mg/kg are administered and 14-day safety data from the last treatment are available) will determine whether dosing will continue for subjects within a cohort and if the investigational product will be administered at the next higher dose level for subjects in the next cohort in Part A or for Cohort 4 in Part B (refer to Section 6.3 for details on the Safety Monitoring Plan).

For subjects in all cohorts, a sigmoidoscopy with biopsy is scheduled at Week 12 to assess improvement in the mucosa from Baseline (Week 0) to Week 12. It is highly recommended that the sigmoidoscopy with biopsy be performed within 7 to 13 days prior to the Week 12 visit. The sigmoidoscopy results from the central reader are required before a subject receives treatment in the OLE/LTE Therapy phase.

### **6.1.2 Long-term Extension Therapy: Week 12 (First Dose) to Week 52**

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 (see Section 6.1.3).

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. 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. Mucosal healing is defined as a mMES of 0 or 1.

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). Refer to Section 8.1.4.2 for additional dosing details in LTE Therapy.

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.

### **6.1.3 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). Refer to Section 8.1.4.2 for additional dosing details in OLE Therapy.

### **6.1.4 Transitioning from the Long-term Extension to the Open-label Extension**

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.

## **6.2 Study Rationale**

In a Phase 1a/1b study (4083-001) in 68 subjects with mild to moderate plaque-type psoriasis, no dose-limiting adverse effects were observed following a single SC injection (1.0 mg/kg) or IV infusion ( $\leq 10$  mg/kg). The current study of KHK4083 in subjects with UC is based on the observation that OX40-bearing lymphocytes have been reported in colonic biopsies of patients with UC. (Stüber, 2000) In sites of mucosal inflammation, the expression of OX40 ligand on gut endothelial and OX40+ cells was increased in the colon and jejunum of patients with IBD. (Souza, 1999)

The 12-week efficacy evaluation for improvement in the mucosa is based on mMES and is the primary efficacy endpoint of this study. The continuation of subjects (i.e., who have evaluable total Mayo Clinic scores and have a clinical response or mucosal healing) in the 40-week OLE/LTE Therapy phase allows for extending the period of treatment and completing assessments for delayed responses, durable clinical response, and durable clinical remission.

## **6.3 Study Safety Monitoring Plan**

All subjects will be assessed regularly for potential occurrence of adverse events (AEs) from the time of signing the informed consent form (ICF) until 16 weeks after the last dose. If consistent mild and/or moderate infusion reactions are observed, the Sponsor may recommend pretreatment of subjects. In the event that any subject experiences an acute infusion reaction considered to be a serious adverse event (SAE), a slower infusion rate for administration of the investigational product and/or a mandatory pre-medication regimen (e.g., anti-emetics, H1 or H2 blockers, and/or corticosteroids) may be introduced. Each investigative site must have trained staff and immediate access to emergency supplies and equipment including, but not limited to, drugs needed to treat a subject in case of a life-threatening emergency.

The Sponsor has primary responsibility for the ongoing medical review of safety data throughout the study.

Recommendations will be made with the input of the Medical Monitor to the Principal Investigator and other appropriate designated staff regarding further conduct of the study. Medical Monitoring meetings will be held on a regular basis to monitor the safety of the subjects and adherence to the protocol (e.g., inclusion and exclusion criteria, concomitant medications, and visits) in addition to the Safety Monitoring Committee meetings described below.

The Safety Monitoring Committee, which recommends dose-escalation and continuation of the study will meet prior to starting each cohort (based upon projected enrollment rate is anticipated to be approximately every 3 months) and as needed during the study. A separate Safety Monitoring Committee Charter will identify the membership and define the specific procedures of the committee.

The Safety Monitoring Committee will evaluate the cumulative safety data available after the first 8 subjects (1.0 mg/kg dose cohort) at Week 4. For subsequent dose escalation, the Safety Monitoring Committee will evaluate the cumulative safety data available after the first 8 subjects at Week 4 with the first 4 subjects at Week 6 for the 3.0 and 10 mg/kg dose cohorts. At each of the timepoints, the committee will assess whether dosing will continue for all subjects and if the investigational product will be administered at the next higher dose level for subjects in the next cohort in Part A or for Cohort 4 in Part B. The Safety Monitoring Committee and Sponsor may dose-reduce cohorts or not escalate to the planned doses based upon review of safety data. The OLE dose will be the same as the dose for that cohort during the induction therapy, unless dose reduction is recommended by the Safety Monitoring Committee and Sponsor.

The safety monitoring plan is as follows:

**Induction Therapy - Part A (Cohort 1):**

- Prior to randomization of the first subject - review rules and reach a consensus;
- When safety data are available on the first 8 of 12 randomized subjects who complete or would have completed Week 4 (~Day 29).

**Induction Therapy - Part A (Cohorts 2 and 3):**

- When safety data are available on the first 8 randomized subjects in a cohort who complete or would have completed Week 4 (~Day 29) with the first 4 subjects in a cohort who complete or would have completed Week 6 (~Day 43).

**Induction Therapy - Part B (Cohort 4):**

- When safety data are available on the first 8 randomized subjects who complete or would have completed Week 6 (~Day 43);
- When safety data are available on all randomized subjects who complete or would have completed Week 12.

**Open-label/Long-term Extension Therapy:**

- When safety data are available on all subjects who complete or would have completed Week 24;

- When safety data are available on all subjects who complete or would have completed Week 36.

If unblinding of a cohort is necessary, the Sponsor's physician, clinical pharmacologist, a biostatistician, and a representative from Drug Safety Surveillance, all not associated with the conduct of the study, will make recommendations for study continuation and design, including dose selection for each cohort.

This study's safety monitoring plan is justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits a comparison of the safety response to KHK4083 under baseline and post-KHK4083 administration conditions in the same subject.
- The design of the safety plan allows a comparison of this study's safety data set with the Phase 1a/1b study (4083-001).
- The safety monitoring follow-ups permit the evaluation of late appearing adverse effects that may emerge or progress after the administration of KHK4083.
- The measures used to assess safety are well-defined and reliable, and the proposed safety analyses are adequate to assess the effects of the administration of KHK4083.

## **6.4 Study Timeframe**

Subsequent to the 4-week Screening Period, the total study participation time is up to 64 weeks from the time of randomization to study completion. The 52-week Treatment Period includes a 12-week Induction Therapy phase and a 40-week OLE/LTE Maintenance Therapy phase. A post-treatment Follow-up Period will be conducted either at Week 16 through Week 26 for subjects who only receive Induction Therapy or at Week 56 through Week 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.

## **6.5 Risks and Benefits to Subjects**

### **6.5.1 Risks**

Subjects receiving investigational product should be monitored carefully for hematologic abnormalities and any applicable dose modification/stopping rules should be followed. In a recently completed clinical study (4083-001) in subjects with psoriasis, no dose-limiting AEs were observed during the 56-day safety assessment periods following single SC (1.0 mg/kg) or IV ( $\leq 3.0$  mg/kg) doses or during a 70-day safety assessment period following an IV dose of 10 mg/kg.

## **6.5.2 Benefits**

The potential benefits of KHK4083 treatment are to improve the mucosa, induce mucosal healing, improve the clinical signs and symptoms of UC, induce a clinical response and remission, and maintain a durable clinical response and durable clinical remission by continuation of therapy.

## **7 SELECTION AND WITHDRAWAL OF SUBJECTS**

Male and female subjects (age:  $\geq 18$  years) with moderately active UC who meet all the Inclusion Criteria and none of the Exclusion Criteria will be eligible for entry into this study.

### **7.1 Procedures for Enrollment**

This multicenter study will be conducted in approximately 60 adult subjects with moderately active UC at approximately 40 investigative sites in the US, Russia, Hungary, Poland, Romania, Serbia and Czech Republic; other countries may be included as needed.

At the Screening visit, the Investigator will review the written ICF with each subject to ensure that the subject understands the study and the study procedures. The subject will read, sign, and date the ICF and other locally applicable documents. A photocopy of the signed ICF must be provided to the subject and the original document retained in the subject's source or study file. No study-related procedures may be performed until the ICF is signed and dated.

The Interactive Response Technology (IRT) system will be used by the Investigator (or designee) for assigning a Subject Identification Number after the ICF is signed and dated.

A subject who was considered a Screen failure and not dosed with investigational product is permitted to be re-screened once due to failure to meet the Inclusion/Exclusion Criteria, whereas subjects with other reasons for lack of randomization may be re-screened twice. This allows for re-screening in the event a subject fails screening because all assessments were not completed within the 28-day screening window. An assigned Subject Identification Number will only be used once; thus, numbers for any Screen failures or non-treated, non-evaluable, or discontinued subjects will not be re-used.

## 7.2 Inclusion Criteria

Subjects may be included in the study if they meet all of the following Inclusion Criteria:

- 1) Subject is able and willing to comply with study procedures, and to adhere to dosing and visit schedules and follow-up procedures as described in the protocol and ICF;
- 2) Subject voluntarily signs/dates an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF in accordance with regulatory and institutional guidelines;  
*Note: Written informed consent must be obtained prior to performing any study-related procedure.*
- 3) Male and female subjects  $\geq 18$  years of age at the time of enrollment;
- 4) Subject has UC that was diagnosed at least 6 months prior to the Screening visit;
- 5) Subject has moderately active UC, defined as:
  - a) Total Mayo Clinic score of 4 to 9 (range: 0 to 12, with higher scores indicating more disease activity);
  - b) Endoscopy subscore (mMES determined by a central reader) of at least 2; and
  - c) Disease that extends  $\geq 15$  cm from the anal verge.
- 6) Subject has had previous treatment (within 5 years prior to Screening) with one or more of the following: corticosteroids, immunosuppressive medications or TNF antagonist therapy that was unsuccessful because of a lack of efficacy response or AEs, as defined below:
  - a) corticosteroids for induction therapy of at least prednisolone-equivalent of 20 mg (or oral budesonide 9 mg) oral daily for 2 weeks or injectable for 1 week, or for maintenance therapy at least two failed attempts to reduce to less than prednisolone-equivalent 10 mg (or oral budesonide 3 mg) oral daily, or a history of intolerance to corticosteroids (including but not limited to hypertension, insomnia, osteopenia, osteoporosis, hyperglycemia, infection or Cushing's syndrome);
  - b) Azathioprine or 6-mercaptopurine of at least 1.5 mg/kg/day or 0.75 mg/kg/day, respectively, for 8 weeks, or a history of intolerance to either agent (including but not limited to nausea, vomiting, abdominal pain, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations, thiopurine methyltransferase genetic mutation, or infection);
  - c) tumor necrosis factor-alpha antagonists for induction therapy with approved anti-TNF products including, but not limited to, infliximab 5 mg/kg IV for 2 doses at least 2 weeks apart, adalimumab 160 mg SC followed by at least 80 mg SC at least 2 weeks apart, and golimumab 200 mg SC followed by at least 100 mg at least 2 weeks apart and anti-TNF biosimilar products with approved dosages for 2 doses at least 2 weeks apart; or as maintenance therapy for recurrence of symptoms despite continued dosing, or history of intolerance

(including but not limited to infusion or injection reactions, demyelination or infection).

- 7) Female subjects who are considered to be women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening and Baseline. WOCBP must agree to use effective contraception, defined as oral contraceptives with one barrier method, or tubal ligation with one barrier method or double barrier method (condom plus spermicide or diaphragm plus spermicide) during the study and for at least 6 months after the last dose of investigational product. Subjects are considered to not be of childbearing potential if they are  $\geq 50$  years of age and without menses for 24 consecutive months and have a follicle-stimulating hormone (FSH) level  $> 25$  mIU/mL (or in postmenopausal range per local laboratory standards); or have undergone a hysterectomy and/or a bilateral salpingo-oophorectomy.  
Egg donation is not permitted while on study medication and for at least 6 months after the last dose of study medication.
- 8) Male subjects (including those who have had a vasectomy) must use adequate contraception (e.g., latex condom, non-latex condom not made of natural animal membrane such as polyurethane condom) during the study and for at least 6 months after the last dose of investigational product.  
Sperm donation is not permitted while on study medication and for at least 6 months after the last dose of study medication.

### **7.3 Exclusion Criteria**

Subjects must be excluded from participating in this study if they meet any of the following Exclusion Criteria:

- 1) Subject, who, for any reason, is judged by the Investigator to be inappropriate for this study, including a subject who is unable to communicate or cooperate with the Investigator, who has/had a psychiatric illness, disability or social situation that may compromise the safety of the subject during the study or affect the ability of the subject to adhere to study procedures;
- 2) Subject has a medical history of clinically significant (as determined by the Investigator or the Sponsor) cardiac, renal, hepatic/biliary (e.g., sclerosing cholangitis), pulmonary, or other medical conditions or is not generally in good health.

Subjects with the history of immunologic, autoimmune or chronic inflammatory disorders (e.g., uveitis, rheumatoid arthritis, ankylosing spondylitis or spondyloarthritis, psoriasis) other than UC or autoimmune connective tissue diseases (e.g., systemic lupus erythematosus, systemic sclerosis) and are well controlled may be included into the trial after consultancy with medical monitor. Subjects with thyroid disorders, vitiligo, and alopecia are eligible for inclusion.

- 3) Subject's UC had failed to respond to:
  - a) Two or more biologic treatments with different mechanisms of action (e.g., infliximab, vedolizumab and golimumab), or
  - b) Three or more anti-TNF biologics, e.g., infliximab, adalimumab;
- 4) Subject requires prescription treatment for UC, except for the stable, oral treatment of UC as follows:
  - a) Aminosalicylates (5-ASA acid or mesalamine  $\leq 4.8$  g/day; sulfasalazine  $\leq 3$  g/day) for at least 14 days prior to the Screening visit; and/or
  - b) Glucocorticoids ( $\leq 20$  mg/day prednisolone or the equivalent, or budesonide  $\leq 9$  mg/day) for at least 14 days prior to the Screening visit (or for 4 weeks if a course of corticosteroids had started at less than 8 weeks prior to Screening visit); and/or
  - c) Azathioprine up to 3 mg/kg/day or 6-mercaptopurine up to 1.5 mg/kg/day for a total treatment period of at least 12 weeks, including 4 weeks of stable treatment, prior to the Screening visit.
- 5) Subject has received any of the following prior treatments or treatments within the specified time:
  - a) Natalizumab, efalizumab or rituximab or other lymphocyte-depleting treatments, including but not limited, to alkylating agents (such as cyclophosphamide or chlorambucil) and total lymphoid irradiation at any time prior to randomization (Baseline visit);
  - b) TNF antagonists within 8 weeks, or 5 half-lives (based on maximum duration but not exceeding 12 weeks), prior to randomization (Baseline visit);
  - c) Vedolizumab within 16 weeks prior to randomization (Baseline visit);
  - d) Methotrexate, cyclosporine, mycophenolate, tacrolimus, thalidomide, or other immune altering drugs within 4 weeks prior to randomization (Baseline visit) (ophthalmologic preparations are permitted);
  - e) 5-ASA enema, or steroid enema or suppository use within 2 weeks prior to randomization (Baseline visit); and/or
  - f) Investigational agents within 8 weeks or 5 half-lives (if pharmacology information is available) prior to randomization (Baseline visit) whichever is longer.
- 6) Subject with recent (within 1 year prior to Screening), suspected or confirmed symptomatic stenosis of the colon, abdominal abscess, or ischemic colitis based on clinical or radiographic data; or who has suspected, confirmed or a history of toxic megacolon; or with any colonic resection, subtotal or total colectomy, ileostomy, or colostomy; or who had any previous surgery for UC or an anticipated requirement for surgery for UC;
- 7) Subject with known colonic dysplasia, adenomas or polyposis;
- 8) Subject had major surgery within 4 weeks prior to Screening or an anticipated requirement for major surgery;

- 9) Subject with enteric pathogens (including *Clostridium difficile*) detected on stool analysis; or *Clostridium difficile* infection within 8 weeks prior to Screening; or intestinal pathogen infection detected within 4 weeks prior to Screening;
- 10) Subject with any of the following hematological and chemistry laboratory values:
  - a) Platelet count < 100,000/mm<sup>3</sup>;
  - b) Neutrophils < 1500/mm<sup>3</sup>;
  - c) Serum creatinine  $\geq$  1.6 mg/dL ( $\geq$  144.4  $\mu$ mol/L);
  - d) Alkaline phosphatase > 3 times the upper limit of normal (ULN);
  - e) AST or ALT > 2 times ULN;
  - f) Total bilirubin > 2 mg/dL, unless due to Gilbert's Syndrome;
  - g) Serum albumin < 3 g/dL;
  - h) Hemoglobin < 9 g/dL;
  - i) Glycated serum hemoglobin A1c  $\geq$  9%.
- 11) Subject has clinically significant cardiac disease (class II, III, or IV of the New York Heart Association [NYHA] classification) (The Criteria Committee of the NYHA Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 1994); unstable angina pectoris; myocardial infarction within 6 months or is post angioplasty or stenting within 6 months; uncontrolled hypertension; or clinically significant abnormality, such as cardiac arrhythmia, on a 12-lead electrocardiogram (ECG) at Screening;
- 12) Subject is pregnant or breastfeeding;
- 13) Subject has had major immunologic reaction (e.g., serum sickness, anaphylaxis, or anaphylactoid reaction);
- 14) Subject is Hepatitis B core antibody or surface antigen positive at Screening and/or Hepatitis C antibody positive with detectable RNA at Screening;
- 15) Subject has a history of human immunodeficiency virus (HIV) positivity, tests positive for HIV at Screening, or has congenital or acquired immunodeficiency;
- 16) Subject has or has had active TB, suspected extra-pulmonary TB, a history of incompletely treated TB, or latent TB or other latent infection. Subjects with latent TB (purified protein derivative [PPD] or interferon gamma release assay [IGRA]) may be included in the study if prophylactic therapy for latent TB is started at least 4 weeks prior to Screening. Subjects with a potentially untreated other infection (clinical findings) are to be excluded.

*Note: Performing of both IGRA and PPD tests in the same subject should be avoided as screening procedures. Positivity of one of the tests cannot be voided by negativity of the other, i.e., subjects with positive PPD and negative IGRA test performed as a part of Screening will be considered TB positive and will be required to start prophylactic anti-TB therapy prior to infusion of investigational product according to local treatment standards. All safety laboratory tests may be repeated. Screening procedures may be extended by 2 weeks.*

- 17) Subject has bacterial infections requiring treatment with oral or parenteral antibiotics (topical antibiotics are allowed), within 2 and 4 weeks, respectively, of the Screening period;
- 18) Subject has a history of systemic opportunistic infection or recurrent infections;
- 19) Subject has malignancy or history of malignancy, except for adequately treated basal cell skin cancer or adequately treated carcinoma in-situ of the cervix without recurrence, and treatment must have been completed at least 5 years before the Screening period;
- 20) Subject who received a bacille Calmette-Guérin (BCG) vaccine within 6 months of randomization or live vaccination (e.g., measles, mumps, rubella [MMR]; herpes zoster; varicella, intranasal influenza; and oral poliomyelitis) within 4 weeks of randomization is to be excluded. Subject is allowed vaccinations of inactivated vaccines (e.g., hepatitis, pneumococcal, meningococcal, tetanus, diphtheria toxoid, acellular pertussis, inactivated polio, human papilloma and influenza – except intranasal influenza);
- 21) Subject with a history of substance abuse within 1 year of Screening; or active marijuana (medicinal or recreational) use or active substance abuse;
- 22) Subject has other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results, as determined by the Investigator;
- 23) Subject who previously participated in a study of KHK4083.  
*Note: A subject who was considered a Screen failure and not dosed with investigational product in the current study (4083-002) is permitted to be re-screened once due to failure to meet the Inclusion/Exclusion Criteria, whereas subjects with other reasons for lack of randomization may be re-screened twice.*

#### **7.4 Additional Criteria to Enroll in Open-label Extension Therapy**

Prior to receiving investigational product (one infusion every 4 weeks) in the OLE, subjects must meet the following criteria:

- 1) Subjects must have completed double-blind Induction Therapy, i.e., at least five of six double-blind treatments, or the subject is already in the double-blind LTE and not beyond Week 28 with a clinical worsening or a flare of disease as defined by the Investigator;
- 2) Subjects must have evaluable total Mayo Clinic scores at Baseline and Week 12;
- 3) Subjects must have been compliant with the protocol (including concomitant medication restrictions); and
- 4) Subjects may have no clinically significant additional risks, as determined by the Investigator or the Sponsor, of treatment with KHK4083.

## **7.5 Withdrawal and Termination Criteria**

In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of compliance with the protocol.

### **7.5.1 Subject Withdrawal**

During the conduct of the study, the Sponsor will review the safety data for trends and signals that would indicate the need for withdrawal of a subject. The Investigator may withdraw a subject from the study for any of the following reasons:

- For any of the specific criteria listed in Section 7.5.3;
- Pregnancy;
- For any reason judged by the Investigator to be inappropriate to continue in the study, including a subject who is unable to communicate or cooperate with the Investigator, who has/had a psychiatric illness, disability or social situation that may compromise the safety of the subject during the study or affect the ability of the subject to adhere to study procedures;
- The study is terminated by the Sponsor;
- Any therapy-related event that is deemed life-threatening, regardless of intensity;
- Protocol noncompliance;
- Withdrawal of consent.

Should a subject decide to withdraw after administration of the investigational product (KHK4083 or placebo), or should the Investigator(s) decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be completed and an explanation given as to why the subject is withdrawing or being withdrawn from the study.

The reason for withdrawal must be collected. If the reason for withdrawal is a clinical AE, whether considered to be related to investigational product or not, the AE must be monitored until the return to the subject's baseline condition or until clinically satisfactory resolution is achieved (e.g., Grade 1 or stable). The clinical course of the AE will be followed according to accepted standards of care or medical practice, even after the end of the period of observation until a satisfactory explanation is found or the Investigator considers it medically justifiable to terminate follow up (e.g., event returned to subject's baseline, Grade 1, or stable).

### **7.5.2 Study or Investigative Site Termination**

The Sponsor reserves the right to terminate the study at any time. Investigators have the responsibility to comply with International Conference on Harmonisation (ICH) E6-Good Clinical Practice (GCP) guidance. The Safety Monitoring Committee (refer to Section 6.3) may recommend termination of the study if the overall risk to subject safety is deemed to be unacceptable, including but not limited to serious or severe infection rates  $\geq 40\%$  in the first cohort of 12 treated subjects (5/12) and similarly in subsequent cohorts. In addition, 2 subjects with two or more Suspected Unexpected Serious Adverse Reactions (SUSARs) of the same System Organ Class (SOC) may result in a recommendation to terminate the study.

In the event the study will be terminated, the Sponsor must promptly inform the hospital or clinic director of all participating institutions, Investigators, and regulatory authorities in writing. The Investigator is responsible for notifying subjects, stopping subject screening and dosing immediately, and providing appropriate medical care. Subjects dosed will be followed for safety for 16 weeks post-treatment and AE resolution. The Sponsor or the IRB/IEC may terminate the study for the following (but not limited to) reasons:

- Important safety findings, such as SAEs, which may influence subjects' well-being; or
- Other newly obtained information or reason(s) that may affect continuation of study.

The Sponsor or the IRB/IEC may terminate an investigative site for the following (but not limited to) reasons:

- Failure of the Investigator to comply with pertinent ICH E6-GCP guidelines and regulations;
- If serious protocol violations occur;
- Submission of knowingly false information from the research facility to the Sponsor, Medical Monitor, or other party involved in the study;
- Failure of the Investigator to enroll subjects into the study at an acceptable rate as agreed to with the Sponsor; or
- Repeated failure to have eCRF data completed and ready for submission to the Sponsor in the agreed-upon time.

### **7.5.3 Criteria for Subject Removal from Treatment and the Study**

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the subject in the study. However, if the Investigator concludes that it is in the best interest of the subject to discontinue administration of the investigational product, including subjects who have not benefited from treatment or should

the subject decide to discontinue study treatment, all efforts will be made to complete and report the observations as thoroughly as possible.

Investigational product administration will be stopped if any of the following events occur:

- Subject experiences a second SUSAR of the same SOC;
- Subject experiences a severe AE that is related to the investigational product;  
*Investigational product administration may be withheld for up to 2 weeks if the subject experiences a severe event in which it is unclear if the event is related to the investigational product. This will allow the Investigator to determine if the event is related to the investigational product prior to removing the subject permanently from the study.*
- Subject experiences a severe, acute infusion reaction despite administration of a prophylactic pre-medication regimen or if the subject experiences anaphylaxis regardless of having received a pre-medication regimen or not. Anaphylaxis has symptomatic bronchospasm and/or allergy-related edema/angioedema as the principal clinical manifestation(s); refer to the clinical diagnostic criteria of anaphylaxis defined in Appendix 5);
- Subject has two consecutive visits during Induction Therapy with a worsening from Baseline in partial Mayo Clinic score of  $\geq 3$  points (e.g., partial Mayo Clinic score of 3 at baseline, 6 at Week 2, and 6 at Week 4) or two consecutive visits during maintenance therapy with a worsening from Week 12 in partial Mayo Clinic score of  $\geq 3$  points at a visit and  $\geq 5$  points at the next visit unless the Investigator, with agreement from the Sponsor, determines that there has not been clinically significant worsening, in which case the subject may continue to receive study medication at that visit (agreement from the Sponsor is to be obtained for each visit);
- Surgery and/or use of prohibited medications are needed to treat the worsening of UC;
- Subject requires a concomitant medication that is prohibited in the study;
- Subject has any clinical AEs, laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject. The Investigator should make a distinction between AEs that may require only interruption of treatment and those that require discontinuation;
- Subject decides to withdraw consent from the study in the absence of a medical need to withdraw as determined by the Investigator;
- Subject is noncompliant in the opinion of the Investigator;
- Administrative reasons; or
- If pregnancy is suspected while the subject is receiving investigational product, the treatment must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the investigational product will be permanently discontinued and the subject withdrawn from the study.

In the case of pregnancy, the Investigator must immediately notify the Sponsor of this event and record the pregnancy on the Pregnancy Surveillance Form. The Sponsor must also be

notified if a partner of a study subject becomes pregnant while the subject was receiving the investigational product. Reasonable attempts will be made to follow the pregnancy to conclusion in order to obtain information regarding the outcome.

#### **7.5.4 End-of-Treatment Visit**

An End-of-Treatment visit must be conducted for all subjects who discontinue from treatment. This visit must occur within 2 weeks or 4 weeks after the last dose of investigational product of Induction Therapy or OLE/LTE Therapy, respectively.

If the subject discontinues during Induction Therapy, the assessments listed in Table 9.1 for End-of-Treatment/Week 12 should be performed at the End-of-Treatment visit. A sigmoidoscopy will be performed at End-of-Treatment/Week 12 if the subject discontinues more than 8 weeks after Baseline visit; the sigmoidoscopy may be performed up to 4 weeks after the last dose of study medication. Post-treatment follow-up visits should subsequently occur 4, 8 and 14 weeks after the End-of-Treatment/Week 12 visit.

If the subject discontinues during OLE/LTE therapy, the assessments listed in Table 9.2 for End-of-Treatment/Week 52 should be performed at the End-of-Treatment visit. A sigmoidoscopy will be performed at End-of-Treatment/Week 52 if the subject discontinues more than 8 weeks after the Week 12 visit; the sigmoidoscopy may be performed up to 8 weeks after the last dose of study medication. Post-treatment follow-up visits should subsequently occur 4, 8 and 12 weeks after the End-of-Treatment/Week 52 visit.

The Investigator must complete all applicable End-of-Treatment visit procedures (e.g., sigmoidoscopy, safety laboratory parameters, ECG, physical examination, vital signs) and applicable eCRF pages for subjects who discontinue treatment and include the reason for discontinuation of treatment.

#### **7.5.5 End-of-Study Visit**

If the subject is withdrawn from the study, and thus no subsequent visits are planned, then the Investigator must complete all applicable final visit procedures (e.g., safety laboratory procedures, ECG, physical examination, vital signs) and applicable eCRF pages for subjects who discontinue treatment and include the reason for discontinuation of treatment. If the subject discontinues during the Induction Therapy, the assessment listed in Table 9.1 for Follow-up 3 should be performed at the End-of-Study visit. If the subject discontinues during OLE/LTE Therapy, the assessments listed in Table 9-2 for Follow-up 3 should be performed at the End-of -Study visit.

If the End-of-Study visit is the same as the End-of-Treatment visit then the End-of-Treatment visit assessments should be performed and the End-of-Treatment visit will also be the End-of-Study (end-of-trial) visit.

Once subjects discontinue participation from the study, they will revert to the care of their usual physician for treatment/management of their condition/disease as appropriate.

## **7.6 Replacement of Subjects**

A subject who withdraws after randomization will not be replaced and may not re-enter the study.

# **8 TREATMENT OF SUBJECTS**

## **8.1 Investigational Product(s)**

KHK4083 investigational product, 100 mg/vial (100 mg/mL, 1-mL label fill), is supplied as a single-use, preservative-free solution for IV infusion. The KHK4083 investigational product is a sterile, non-pyrogenic, clear to slightly opalescent, colorless to slightly brownish-yellow solution essentially free of visible particulates. The product is formulated at a concentration of 100 mg/mL in L-histidine, D-sorbitol, L-methionine, Polysorbate 80, and hydrochloric acid, pH 5.5. The 100 mg/vial presentation is contained in 3-mL clear, United States Pharmacopoeia (USP) Type I glass vials that are stoppered with rubber stoppers and sealed with aluminum seals. A volume of 1.3 mL of KHK4083 investigational product is filled per vial. A 0.3-mL over-fill is included in each vial to account for vial, needle, and syringe holdup.

Placebo for KHK4083 is supplied in the same container closure system and contains the same deliverable volume and excipients as KHK4083 investigational product without the active ingredient.

### **8.1.1 Recommended Storage and Use Conditions**

The investigational products (KHK4083 and placebo) should be stored in a secure, limited-access area at a temperature of 2°C to 8°C (36°F to 46°F) and protected from light. The vials should not be shaken.

Guidance on the dilution procedure and recommended storage conditions for diluted solutions of KHK4083 investigational product and placebo can be found in the Pharmacy Manual.

## **8.1.2 Investigational Product Destruction**

Upon completion or termination of the study, all vials (used and unopened) of KHK4083 and placebo must be destroyed upon authorization by the Sponsor and according to the investigative site's biohazardous waste procedures and local regulations.

It will be the Investigator's responsibility to arrange for disposal of all investigational products with containers, provided that procedures for proper disposal have been established according to applicable regulations and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

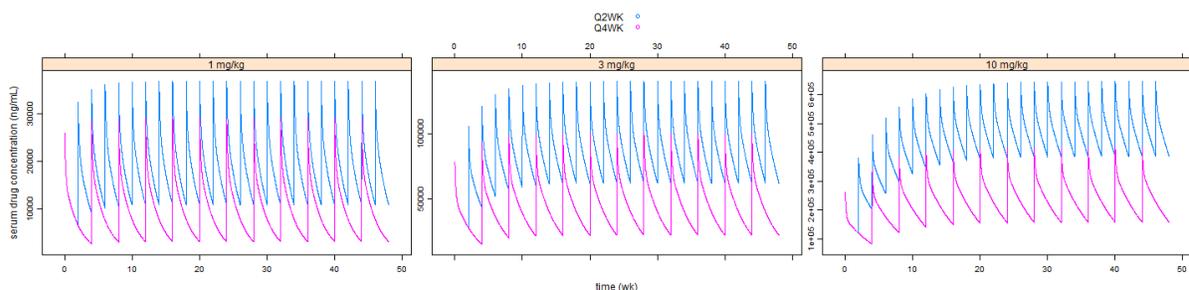
A copy of the certificate of destruction must be placed in the Sponsor's Trial Master File. Refer to the Pharmacy Manual for additional details on the destruction of investigational product.

## **8.1.3 Dosage and Administration**

### **8.1.3.1 Selection of Doses**

The first human study (Study 4083-001, A Single-Ascending-Dose Phase 1a Study and Placebo-Controlled, Double-blind, Single-Ascending-Dose Phase 1b Study of an Anti-OX40 Monoclonal Antibody [KHK4083] in Subjects with Mild-Moderate Plaque-Type Psoriasis) was conducted in 68 subjects. Dose escalation of KHK4083 was started at 0.003 mg/kg (Cohort 1), followed by single ascending dose cohorts of 0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg (Cohorts 2 - 7) administered as 60-minute IV infusions. A single SC dose of 1.0 mg/kg (Cohort 8) also was administered. This study was amended to include an additional single ascending dose cohort of 10 mg/kg (Cohort 9) administered as a 120-minute IV infusion. The doses selected for the current study (4083-002) are based on the Phase 1a/1b study, which showed that KHK4083 was well tolerated and there were no dose-limiting adverse effects at doses  $\leq$  10 mg/kg.

The PK data from IV dose Cohorts 1 to 7 and Cohort 9 were analyzed using a non-linear-mixed-effect modeling technique. Significant departure from dose proportionality was observed as the terminal elimination rate decreased with increasing dose. This is possibly related to target-mediated drug disposition. Simultaneous modeling of all PK data was performed. A two-compartmental PK disposition model described PK profiles well with apparent effect of dose on clearance. Hence, trial simulations were performed for the present Phase 2 multiple ascending dose study of KHK4083 for administration every 2 weeks or every 4 weeks at 1.0, 3.0, and 10 mg/kg as a 60-minute ( $\pm$  10 minutes) IV infusion. Simulated PK profiles are shown in Figure 8.1-1.

**Figure 8.1-1 Simulated Pharmacokinetic Profiles Following Multiple-dose Administration of KHK4083 for Study 4083-002**

The following PK parameters were estimated based on the simulation outputs: trough simulated concentration at the end of steady-state dosing interval ( $C_{\min-ss}$ ), maximum simulated concentration at steady-state dosing interval  $C_{\max-ss}$ , area under the curve at steady state during a dosing interval ( $AUC_{2wk}$ ), accumulation ratio calculated as  $AUC_{2wk}$  for the last interval divided by  $AUC_{2wk}$  for the first interval ( $R_{ac}$ ). The results are shown in Table 8.1.3-1.

**Table 8.1.3-1 Simulated Pharmacokinetic Parameters for the KHK4083 Once Every 2 Weeks Dosing Regimen**

<b>KHK4083 Dose (mg/kg)</b>	<b><math>AUC_{2wk}</math> (<math>\mu\text{g}\cdot\text{hr}/\text{mL}</math>)</b>	<b><math>R_{ac}</math></b>	<b><math>C_{\min-ss}</math> (<math>\mu\text{g}/\text{mL}</math>)</b>	<b><math>C_{\max-ss}</math> (<math>\mu\text{g}/\text{mL}</math>)</b>	<b><math>t_{1/2}</math> (days)</b>
1.0	6230	1.62	10.9	36.9	10.5
3.0	29200	2.17	62.1	140.0	16.3
10	159000	3.14	385.0	645.0	26.2

$AUC_{2wk}$ =area under the concentration-time curve at 2 weeks post-dose;  $C_{\max-ss}$ =maximum simulated serum concentration at steady state;  $C_{\min-ss}$ =trough simulated concentration at the end of the dosing interval at steady state;  $R_{ac}$ =accumulation ratio;  $t_{1/2}$ =terminal elimination half-life.

In the 26-week GLP toxicology study in male and female cynomolgus monkeys (SBL303-104) at the NOAEL of 30 mg/kg, the mean  $AUC_{0-2wk}$  and  $C_{\max}$  were 301500  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 1510  $\mu\text{g}/\text{mL}$ , respectively, after the 13th dose (i.e., steady state). The safety margins ( $AUC_{0-2wk}$  from the monkey NOAEL/ $AUC_{2wk}$  simulated in humans) were 48.4, 10.3, and 1.9 at 1.0, 3.0, and 10 mg/kg, respectively (Table 8.1.3-2).

In the 4-week GLP toxicology study in male and female cynomolgus monkeys (SBL303-081) at the NOAEL of 100 mg/kg, the mean  $AUC_{0-\infty}$  and  $C_{\max}$  were 607000  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 5345  $\mu\text{g}/\text{mL}$ , respectively, after the first dose. The safety margins ( $AUC_{0-\infty}$  from the monkey NOAEL/ $AUC_{2wk}$  simulated in humans) were 97.4, 20.8, and 3.8 at 1.0, 3.0, and 10 mg/kg, respectively (Table 8.1.3-2).

**Table 8.1.3-2 Safety Margins for the Planned KHK4083 Doses**

KHK4083 Dose (mg/kg)	26-week GLP Toxicology Study <sup>a</sup>		4-week GLP Toxicology Study <sup>b</sup>	
	Safety Margin for AUC <sub>2wk</sub>	Safety Margin for C <sub>max-ss</sub>	Safety Margin for AUC <sub>2wk</sub>	Safety Margin for C <sub>max-ss</sub>
1.0	48.4	40.9	97.4	144.9
3.0	10.3	10.8	20.8	38.2
10	1.9	2.3	3.8	8.3

a: In the 26-week GLP toxicology study in male and female cynomolgus monkeys (SBL303-104), at the NOAEL of 30 mg/kg, the mean AUC<sub>0-2wks</sub> and C<sub>max</sub> were 301500 µg·hr/mL and 1510 µg/mL, respectively, after the 13th dose. Safety Margin=AUC<sub>0-2wk</sub> from monkey NOAEL/AUC<sub>2wk</sub> simulated in humans. Safety Margin=C<sub>max</sub> from monkey NOAEL/C<sub>max</sub> simulated in humans.

b: In the 4-week GLP toxicology study in male and female cynomolgus monkeys (SBL303-081), at the NOAEL of 100 mg/kg, the mean AUC<sub>0-∞</sub> and C<sub>max</sub> were 607000 µg·hr/mL and 5345 µg/mL, respectively, after the first dose. Safety Margin=AUC<sub>0-∞</sub> from monkey NOAEL/AUC<sub>2wk</sub> simulated in humans; Safety Margin=C<sub>max</sub> from monkey NOAEL/C<sub>max-ss</sub> simulated in humans.

AUC<sub>2wk</sub>=area under the concentration-time curve at 2 weeks post-dose; AUC<sub>0-∞</sub>= area under the serum drug concentration-time curve from 0 to infinity; C<sub>max-ss</sub>=maximum observed serum concentration at steady state; GLP=Good Laboratory Practice; NOAEL=no-observed-adverse-effect level.

The safety margins calculated based on C<sub>max</sub> are comparable to the safety margins calculated based on AUC<sub>2wk</sub>. As the Phase 2 study is to reach the PK exposure at the NOAEL dose level, and the 1.0, 3.0, and 10 mg/kg doses given every 2 weeks or every 4 weeks are expected to have overall PK exposure lower than the NOAEL, the selected doses are expected to be a safe dose for this clinical study.

### 8.1.3.2 Administration

Treatment will be administered on an outpatient basis. The minimum IV infusion time will be 60 minutes (± 10 minutes).

### 8.1.3.3 Infusion Reactions

This study must only be performed in medical facilities with the necessary equipment and medications, and staff trained in their use, readily available to manage potential acute infusion reactions, including anaphylactic reactions.

No pre-medication (e.g., anti-emetic; 5HT<sub>3</sub> blocker; histamine H<sub>1</sub> and/or H<sub>2</sub> blocker(s); corticosteroid) is planned to be routinely/prophylactically administered prior to KHK4083 infusion in this study. However, the administration of therapeutic mAbs, even those that are humanized or fully human, may be associated with acute infusion reactions, especially with the first infusion. Therefore, each subject must be carefully monitored at the investigative site for signs of acute, potential dose-limiting infusion reactions during and for at least 3 hours

following the completion of the first and second IV infusions of investigational product in both phases, and for at least 1 hour following all other IV infusions. In addition, a phone call to each subject will be conducted at approximately 48 to 72 hours following the completion of the first and second infusions for any subject who does not return for a visit at the investigative site.

Acute infusion reactions should not be classified as anaphylaxis unless symptomatic bronchospasm and/or allergy-related edema/angioedema is/are the principal clinical manifestation(s). (Refer to diagnostic criteria for anaphylaxis in Appendix 5). Signs and symptoms of acute infusion reactions usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion. Acute infusion reactions should be classified by intensity (i.e., mild, moderate, or severe) of the AE. Refer to Section 10.6.7.1 for reporting an infusion reaction including descriptions of specific symptoms observed or reported by the subject.

Although mild infusion reactions require no intervention and no interruption of the infusion, investigators are permitted to interrupt the infusion for mild reactions, observe the subject for resolution of any signs/symptoms, and restart the infusion at one-half the infusion rate originally prescribed if the reaction substantially resolves. The rate of the remaining infusion may be gradually escalated to the originally prescribed rate based on the subject's subsequent tolerance and Investigator judgment. For subjects who continue treatment, subsequent infusion(s) may be recommended to be administered at a slower infusion rate.

If a moderate infusion reaction occurs, stop the infusion for at least 15 to 30 minutes. Paracetamol orally and diphenhydramine 50 mg IV or an equivalent anti-histamine may be administered. If symptoms abate, re-start the infusion at one-half the previous rate; if symptoms recur, permanently discontinue the infusion. For reactions that do not abate after 30 minutes, worsen or recur, the Investigator should use their medical judgment to consider additional medical measures.

For any subject experiencing an acute infusion reaction of severe intensity, the infusion must be immediately discontinued and the subject must receive immediate medical/nursing assessment and indicated supportive management per the institutional standard of care and local Investigator judgment until the signs/symptoms of the reaction have resolved.

If consistent mild and/or moderate infusion reactions are observed, the Sponsor (i.e., Medical Monitor and/or a representative from Drug Safety Surveillance) and the Investigator (or designee) may recommend the pretreatment of subjects or a slower infusion rate. In the event that any subject experiences an acute infusion reaction considered to be an SAE, there

may be a decision to introduce, for all subjects, a slower infusion rate for administration of the investigational product, and/or a mandatory pre-medication regimen (e.g., anti-emetics; H1 or H2 blockers; and/or corticosteroids), and/or dose-reduction in a cohort.

#### **8.1.3.4 Dose Modifications**

Management of severe or intolerable adverse reactions due to study treatment may require concurrent therapy, dose omission, prolonged infusion time, or temporary withholding or permanent discontinuation of treatment. No dose reduction should be planned for subsequent doses for an individual subject.

Doses chosen for each cohort, as determined by the Safety Monitoring Committee and Sponsor, may result in dose reduction for all subjects enrolled in a cohort.

#### **8.1.4 Treatment Period (Weeks 0 to 52)**

The 52-week Treatment Period (last dose Week 48) includes double-blind Induction Therapy over 12 weeks followed by OLE/double-blind LTE Therapy over 40 weeks. Subjects will continue in the study for 16 weeks after the last infusion associated with the subject's treatment period for on-site post-treatment assessments (refer to Figure 6.1-1 for overall study design). No other investigational or commercial agents or therapies other than KHK4083 and placebo and those described in Section 8.5 may be administered with the intent to treat the subject's UC.

##### **8.1.4.1 Induction Therapy: Weeks 0 to 12 (Last Dose: Week 10)**

Double-blind Induction Therapy (12 weeks) comprises Part A (Cohorts 1 - 3) for IV administration of multiple ascending doses of KHK4083 or placebo; and Part B (Cohort 4) for IV administration of the recommended dose of KHK4083 or placebo. Subjects in Part A are not allowed to participate in Part B of Induction Therapy. Select Sponsor personnel will be unblinded after the last subject completes Induction Therapy (refer to Section 8.4 for details).

Subjects in each cohort will be randomized in a 3:1 ratio to receive KHK4083 or placebo. Each subject in each cohort (Cohorts 1 - 4) will be administered one IV infusion of KHK4083 or placebo once every 2 weeks for a total of 6 treatments, i.e., Day 1 (Week 0), Day 15 (Week 2), Day 29 (Week 4), Day 43 (Week 6), Day 57 (Week 8), and Day 71 (Week 10).

- **Induction Therapy Part A (Cohorts 1 - 3):** 36 subjects (12 subjects/cohort) will be administered investigational product, i.e., 27 subjects (9 subjects/cohort) will receive KHK4083 and 9 subjects (3 subjects/cohort) will receive placebo once every 2 weeks (Weeks 0 to 10) as follows:

Cohort 1: 1.0 mg/kg or placebo

Cohort 2: 3.0 mg/kg or placebo

Cohort 3: 10 mg/kg or placebo

The cumulative safety data available after the first 8 of 12 subjects randomized in Cohort 1 will be evaluated by the Safety Monitoring Committee at Week 4 (~Day 29) to assess whether dosing will continue for subjects within Cohort 1 and if investigational product will be administered at the next higher dose level for subjects in Cohort 2. For Cohorts 2 and 3, the cumulative safety data available after the first 8 subjects in each cohort at Week 4 (~Day 29) and the first 4 subjects in each cohort at Week 6 (~Day 43) will be evaluated for continuation of all of the subjects and for dose escalation in the next cohort, i.e., Cohort 3 in Part A and Cohort 4 in Part B, respectively. The Safety Monitoring Committee and Sponsor may dose-reduce cohorts or not escalate to the planned doses based upon review of safety data (refer to Section 6.3).

- **Induction Therapy Part B (Cohort 4):** The recommended KHK4083 dose (one of three dose levels in Cohorts 1 - 3) is selected based on the safety data from Part A. At least 24 subjects will be administered the recommended dose of KHK4083 (18 subjects) or placebo (6 subjects) once every 2 weeks (Weeks 0 to 10) in Cohort 4.

For subjects in all cohorts, a sigmoidoscopy with biopsy will be performed at Week 12 to assess improvement in the mucosa based on a mean change in the mMES from Baseline (Week 0) to Week 12. It is highly recommended that the sigmoidoscopy with biopsy be performed within 7 to 13 days prior to the Week 12 visit.

#### **8.1.4.2 Open-label/Long-term Extension Maintenance Therapy: Week 12 (First Dose) to Week 52**

All subjects who qualify and continue double-blind LTE or start open-label maintenance therapy will be administered one KHK4083 or placebo (LTE) or one KHK4083 (OLE) IV infusion at Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 for a total of 10 additional treatments followed by an End-of-OLE/LTE Therapy visit at Week 52, and then proceed to the OLE/LTE Therapy Follow-up Period (Week 56 through Week 64). The treatment at Week 12 will be administered at the scheduled visit or within 7 days after Week 12. The OLE dose will be the same as the dose for that cohort during the induction therapy, unless dose-reduction is recommended by the Safety Monitoring Committee and Sponsor (see Section 6.3).

During OLE/LTE Therapy, corticosteroid (glucocorticoid) dosages of prednisolone or its equivalent will be permitted to be tapered (decreasing by up to 2.5 mg/day per week) and other concomitant medications for UC may be tapered. Bolus or “rescue” treatment with systemic corticosteroids or topical corticosteroid enemas or suppositories (in addition to the dose of oral corticosteroids at Screening) is permitted only after Week 12 evaluations are

complete. A sigmoidoscopy with biopsy will be performed at the End-of-OLE/LTE Therapy visit at Week 52 or within 21 days prior to Week 52.

### **8.1.5 Post-treatment Follow-up Period**

Post-treatment Follow-up assessments will continue for 16 weeks after the last infusion associated with the subject's treatment period. For subjects who only receive Induction Therapy (i.e., last dose at Week 10 and do not continue in OLE/LTE Therapy), the Post-treatment Follow-up visits will be at Weeks 16, 20, and 26. For all subjects who receive both Induction Therapy and OLE/LTE Therapy (last dose at Week 48), the Post-treatment Follow-up visits will be at Weeks 56, 60, and 64. Subjects removed from the study for AEs will be followed until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved. The date of the subject's last post-treatment study visit will be considered the End-of-Study date.

## **8.2 Method of Numbering Subjects and Assigning Subjects to Treatment Cohorts or Randomization**

After a subject meets all study eligibility requirements at Screening (refer to Section 7.1 for enrollment procedures), the 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. Subjects who received study medication in Part A are not allowed to participate in Part B.

At the end of Induction Therapy, subjects who meet all study eligibility requirements described in Section 7.4 will start receiving open-label KHK4083 at the same dose for that subject's cohort. Subjects who previously met all study eligibility requirements and entered the LTE will continue to receive KHK4083 or placebo during LTE Therapy phase; subject in the LTE may be eligible for the OLE up to Week 28 as described in Section 6.1.4.

## **8.3 Blinding During the Double-blind Treatment Period (Induction Therapy and Long-term Extension Therapy)**

The subject and Investigator (or investigative site personnel) 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 in Section 8.4.

An assigned pharmacist (or qualified designee) at each investigative site will be unblinded and responsible for preparing the appropriate treatment based on the treatment assignment by the IRT system. The unblinded pharmacist (or qualified designee) will ensure that the investigational product administered to each subject is labeled such that the treatment identity cannot be determined.

#### **8.4 Unblinding During the Treatment Period and After Induction Therapy and Long-term Extension Therapy**

A subject's treatment assignment should only be unblinded by the Investigators and/or Sponsor's Medical Monitor when knowledge of the treatment is essential for the further management of the subject or may impact the safety of subjects in current and/or subsequent cohorts. Unblinding for any other reason will be considered a protocol violation.

The Investigators are strongly encouraged to contact the Medical Monitor before unblinding any subject's treatment assignment. However, the Investigator may unblind for safety reasons without prior notification, but must contact the Medical Monitor within one business day after the event and must document the unblinding in the subject's source records together with a completed SAE form. Any instance of unblinding will be reported in the clinical study report.

The Investigator or the designee who breaks the blind must record the date and the reasons as appropriate. In such cases, treatment with the investigational product must be stopped and the Sponsor must be contacted immediately to determine whether the subject should be withdrawn from the study. Every attempt should be made to contact the Sponsor before the blind is broken.

The study will be unblinded to select personnel from the Sponsor (or consultants acting on behalf of KKD) and/or from participating Contract Research Organizations. The individuals will be identified in the Blinding Plan and Unblinding Processes for Study 4083-002. The study will be blinded to all other study personnel/consultants, investigative site personnel, and study subjects.

After the last subject completes Part B of Induction Therapy, the study will be unblinded to additional select Sponsor personnel. The study will be unblinded to all study

personnel/consultants following database lock after the last subject completes the last follow-up visit.

## 8.5 Prior and Concurrent Therapy

All medications (including prescription, non-prescription and supplements) for treatment of UC taken within 6 months prior to Screening; any other medication taken 1 month prior to Screening; and any concomitant medications (including tracking probiotic usage) during the study will be collected. For all biologic treatments, the reason for discontinuation should be collected at Screening. Combination medications should be recorded by trade name.

Stable doses of the following concomitant medications are permitted for UC treatment during the study as specified below:

- Aminosalicylates (5-ASA or mesalamine  $\leq 4.8$  g/day; sulfasalazine  $\leq 3$  g/day) for at least 14 days prior to the Screening visit; and/or
- Oral glucocorticoids,  $\leq 20$  mg/day prednisolone or the equivalent, or budesonide  $\leq 9$  mg/d for at least 14 days prior to the Screening visit (or for 4 weeks if a course of corticosteroids had started at less than 8 weeks prior to Screening visit); and/or
- Azathioprine up to 3 mg/kg/day or 6-mercaptopurine up to 1.5 mg/kg/day for a total treatment period of at least 12 weeks, including 4 weeks of stable treatment, prior to the Screening visit.

Supportive therapy to manage symptoms or AEs is acceptable. Daily, chronic antidiarrheals should not be taken.

One bolus or “rescue” treatment for up to 7 days with each of the following: systemic corticosteroids or topical corticosteroid enemas or suppositories (in addition to the dose of oral corticosteroids at Screening) is permitted only after Week 12 evaluations are complete. Topical anti-inflammatory agents may be permitted only after Week 12 evaluations are complete and application must be withheld for at least 2 weeks prior to the sigmoidoscopy at Week 52/End-of-Treatment visit.

Dose reductions of concurrent medications are permitted for AEs from Baseline through the end of the study as allowed by the protocol. Other dose adjustments of concurrent medications (including corticosteroids and other treatments for UC) are permitted after the Week 12 visit (per Investigator’s judgment), i.e., during OLE/LTE Therapy and the Induction Therapy and OLE/LTE Therapy Follow-up Periods. After the Week 12 visit, corticosteroid (glucocorticoid) dosages of prednisolone or its equivalent may be tapered by approximately 2.5 mg/day per week, at the Investigator’s discretion. Subjects who have recurrence of clinical symptoms may increase their chronic ( $> 7$  days) dose of corticosteroids and other

treatments for UC may increase up to 110% of the original dose at the start of Induction Therapy.

### **8.5.1 Prohibited Treatment**

During Screening and Induction Therapy, subjects are not permitted to receive rescue therapy for UC including increases in corticosteroids or other medications for UC treatment, except as specified above (Section 8.5).

During Screening, Induction Therapy, and OLE/LTE Therapy, subjects are not permitted to receive any additional experimental therapy or any other therapy to treat the UC, except as specified above. The following is a list of specific prohibited treatments:

- B-cell depleting agents including vedolizumab, natalizumab, efalizumab or rituximab or other lymphocyte-depleting treatments, including but not limited to alkylating agents (such as cyclophosphamide or chlorambucil) and total lymphoid irradiation;
- Methotrexate, cyclosporine, mycophenolate, tacrolimus, thalidomide, or other immune altering drugs; (*Note: ophthalmologic preparations are permitted.*)
- TNF antagonists.

The above prohibited treatments are permitted during the Induction Therapy Follow-up Period and OLE/LTE Therapy Follow-up Period of the study.

Some medications, such as nonsteroidal anti-inflammatory drugs, may need to be administered or held prior to a sigmoidoscopy with biopsy. Those will be detailed in a sigmoidoscopy manual.

## **8.6 Treatment Compliance**

The Investigator is required to ensure compliance with respect to the KHK4083 (or placebo) dosing schedule required by the protocol. At least five of six IV infusions of investigational product are required to be administered during Induction Therapy for treatment compliance in this study. At least half of the IV infusions of investigational product are required to be administered during OLE/LTE Therapy for treatment compliance in this study.

### **8.6.1 Study Visit Outside of Planned Scheduled - Delay in Dosing**

During Induction Therapy, investigational product (KHK4083 or placebo) will be administered every 2 weeks, for a total of 6 doses. A visit window,  $\pm 2$  days at Week 2, and  $\pm 4$  days for all other doses, has been defined. If the study visit/dosing does not occur during the planned visit window, investigational product should not be administered at the visit and

the next dose should be administered at the next visit. KHK4083 or placebo should not be administered less than 6 days from the previous dosing.

## **9 STUDY PROCEDURES**

It is important to maintain the visit structure as accurately as possible. Whenever an adjustment to this structure is necessary, the date of the adjusted visit should occur within the number of days (before or after) specified in the planned schedules for Screening, Induction Therapy, and Induction Therapy Post-treatment Follow-up Period (refer to Study Schedule of Events, Table 9-1) and for OLE/LTE Therapy and OLE/LTE Therapy Post-treatment Follow-up Period (refer to Study Schedule of Events, Table 9-2). The timing of any subsequent visits should be scheduled to maintain the visit structure relative to the first day that investigational product was administered.

Screening evaluations used to determine the subject's study eligibility must be completed within the Screening Period (Day -28 to Day -1) prior to starting treatment on Day 1 (Week 0) unless otherwise specified. Written informed consent must be obtained prior to any study-specific procedures. Results of all Screening evaluations must be reviewed by the Investigator or his/her designee to ensure that all eligibility criteria have been satisfied prior to randomization. For subjects who complete double-blind Induction Therapy and are eligible at Week 12 to receive treatment, additional criteria are required for enrollment in OLE/LTE Therapy (refer to Section 7.4 for the list of criteria).

All efficacy, PK, PD, immunogenicity, and safety measurements obtained during the course of the study are summarized in Table 9-1, Table 9-2, Table 10.4.1-1, and Table 10.4.1-2.

**Table 9-1 Study Schedule of Events - Screening, Induction Therapy, and Follow-up Period**

Procedure	Screening Day -28 to Day -1	Treatment Period - Double-blind Induction Therapy: Weeks 0 to 12 (Last dose at Week 10) <sup>a</sup> (All Randomized Subjects)							Induction Therapy Post-treatment Follow-up Period for Subjects Not Enrolling in OLE Therapy		
		Baseline						End-of- Induction Therapy	Follow- up 1	Follow- up 2	Follow- up 3
		Week 0 Day 1	Week 2 ± 2 days	Week 4 ± 4 days	Week 6 ± 4 days	Week 8 ± 4 days	Week 10 ± 4 days	End-of- Treatment Week 12 ± 4 days	Week 16 ± 7 days	Week 20 ± 7 days	End-of- Study Week 26 ± 7 days
Written Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Medical, Diet & Surgical History/ Demographics	X										
Physical Examination <sup>b</sup>	X	X						X			
Brief Physical Examination <sup>c</sup>			X	X	X	X	X		X	X	X
Vital Signs <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X	X	X	X
Height	X										
12-lead ECG	X	X <sup>e</sup>				X <sup>e</sup>	X <sup>e</sup>				
Hematology (CBC with diff & platelets)	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry Profile	X	X	X	X	X	X	X	X	X	X	X
Coagulation Profile	X	X						X			
Multiplex-31 Assay <sup>f</sup>		X	X					X			
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Serum FSH <sup>g</sup>	X										
Serum Pregnancy <sup>g</sup>	X										
Urine Pregnancy <sup>g</sup>		X		X		X		X	X	X	X
Urine Drug Screen	X										

**Table 9-1 Study Schedule of Events - Screening, Induction Therapy, and Follow-up Period**

Procedure	Screening  Day -28 to Day -1	Treatment Period - Double-blind Induction Therapy: Weeks 0 to 12 (Last dose at Week 10) <sup>a</sup> (All Randomized Subjects)							Induction Therapy Post-treatment Follow-up Period for Subjects Not Enrolling in OLE Therapy		
		Baseline						End-of- Induction Therapy	Follow- up 1	Follow- up 2	Follow- up 3
		Week 0 Day 1	Week 2 ± 2 days	Week 4 ± 4 days	Week 6 ± 4 days	Week 8 ± 4 days	Week 10 ± 4 days	End-of- Treatment Week 12 ± 4 days	Week 16 ± 7 days	Week 20 ± 7 days	End-of- Study Week 26 ± 7 days
Stool Enteric Pathogens (including <i>Clostridium difficile</i> )	X							X			
Hemoglobin A1c	X										
HIV Test; Hepatitis B (core antibody or surface antigen); Hepatitis C antibody	X										
PPD (or QuantiFERON)- TB <sup>h</sup>	X										
Delayed-type Hypersensitivity Skin Test <sup>i</sup> (US and other selected countries)	X						X				
Randomization		X									
Diary Training	X										
Partial Mayo Clinic Score (without sigmoidoscopy, includes review of diary) with Physician's Global Assessment		X	X	X	X	X	X	X	X	X	X

**Table 9-1 Study Schedule of Events - Screening, Induction Therapy, and Follow-up Period**

Procedure	Screening  Day -28 to Day -1	Treatment Period - Double-blind Induction Therapy: Weeks 0 to 12 (Last dose at Week 10) <sup>a</sup> (All Randomized Subjects)							Induction Therapy Post-treatment Follow-up Period for Subjects Not Enrolling in OLE Therapy		
		Baseline						End-of- Induction Therapy	Follow- up 1	Follow- up 2	Follow- up 3
		Week 0 Day 1	Week 2 ± 2 days	Week 4 ± 4 days	Week 6 ± 4 days	Week 8 ± 4 days	Week 10 ± 4 days	End-of- Treatment Week 12 ± 4 days	Week 16 ± 7 days	Week 20 ± 7 days	End-of- Study Week 26 ± 7 days
Flexible Sigmoidoscopy with biopsy for mMES, UCEIS, modified Baron score & total Mayo Clinic score (includes review of diary)	X (within 7 to 28 days prior to first dose)							X <sup>j</sup> (recommend 7 to 13 days prior to Week 12 LTE dosing)			
IBDQ		X	X	X	X	X	X	X	X	X	X
Fecal Calprotectin <sup>k</sup>		X	X					X			
wr-CRP Assay		X	X	X	X	X	X	X			X
Pharmacokinetics		For PK Sample Collection Schedule Refer to Table 10.4.1-1 for Cohorts 1 - 3 during Induction Therapy (Part A) and LTE and Table 10.4.1-2 for Cohort 4 during Induction Therapy (Part B) and LTE									
Anti-KHK4083 Antibodies <sup>l</sup>		X	X	X	X	X	X	X	X	X	X
Flow Cytometry		Refer to Table 10.4.1-1 for Cohorts 1 - 3 and Table 10.4.1-2 for Cohort 4									
Future Biomarker Analyses (whole blood) <sup>m</sup>		X	X					X			X
Adverse Events <sup>n</sup>	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration <sup>a</sup> <b>On-site (plus phone call) Post-infusion Monitoring Required<sup>p</sup></b>		X	X	X	X	X	X				

**Table 9-1 Study Schedule of Events - Screening, Induction Therapy, and Follow-up Period**

Procedure	Screening	Treatment Period - Double-blind Induction Therapy: Weeks 0 to 12 (Last dose at Week 10) <sup>a</sup> (All Randomized Subjects)							Induction Therapy Post-treatment Follow-up Period for Subjects Not Enrolling in OLE Therapy		
	Day -28 to Day -1	Baseline						End-of- Induction Therapy	Follow- up 1	Follow- up 2	Follow- up 3
		Week 0 Day 1	Week 2 ± 2 days	Week 4 ± 4 days	Week 6 ± 4 days	Week 8 ± 4 days	Week 10 ± 4 days	End-of- Treatment Week 12 ± 4 days	Week 16 ± 7 days	Week 20 ± 7 days	End-of- Study Week 26 ± 7 days
Determine if Eligible for OLE at Week 12								X			

**Footnotes to Table 9-1.**

- a: Induction Therapy Dosing Regimen: Part A Cohorts 1 - 3 (KHK4083: 1.0, 3.0, and 10 mg/kg or placebo) once every 2 weeks (Weeks 0 to 10); and Part B Cohort 4 (KHK4083: recommended dose, i.e., one of three dose levels in Cohorts 1 - 3 based on the safety data from Part A, or placebo) once every 2 weeks (Weeks 0 to 10).
- b: Complete physical examinations include general appearance and examination of the HEENT and body systems (cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, and skin).
- c: Brief physical examinations only include the HEENT, cardiovascular, respiratory, and abdominal examinations.
- d: Vital signs include systolic and diastolic blood pressure, radial pulse, respiration rate, and oral body temperature.
- e: Perform ECG pre-dose and at the end of infusion.
- f: If the subject does not continue in OLE Therapy, a sample for the multiplex-31 assay will also be collected at one of the follow-up visits.
- g: Female subjects considered to be women of childbearing potential must have a negative pregnancy test at Screening and Baseline. Subjects are considered to not be of childbearing potential if they are ≥ 50 years of age and without menses for 24 consecutive months; have an FSH level > 25 mIU/mL (or in postmenopausal range per local laboratory standards); or have undergone a hysterectomy and/or a bilateral salpingo-oophorectomy.
- h: Subjects with a low risk of an infection only need an interferon gamma release assay.
- i: For the delayed-type hypersensitivity test, the skin testing site will be read within 48 to 72 hours following intradermal injection of the *Candida albicans* antigen. The largest diameter of induration will be measured in mm and collected.
- j: If the subject discontinues more than 8 weeks after the Baseline visit, a sigmoidoscopy must be performed at End-of-Treatment. The sigmoidoscopy may be performed up to 4 weeks after the last dose of study medication.
- k: Fecal calprotectin concentration, which is usually elevated in subjects with moderately active UC, will be measured. Fecal samples will be collected as specified in the stool collection instruction section of the laboratory manual.
- l: Samples for anti-KHK4083 antibodies must be taken prior to dosing and taken at the same time as pre-dose PK samples shown in Table 10.4.1-1 and Table 10.4.1-2.
- m: Whole blood will be collected and stored (frozen) for potential exploratory biomarker analyses in the future at: Baseline (Week 0), Week 2, Week 12 (End-of-Induction Therapy), and Induction Therapy Post-treatment Follow-up 3 visit (if the subject does not continue in OLE Therapy).
- n: The collection of adverse event information should commence following the subject’s written consent to participate in the study.

**Footnotes to Table 9-1.(cont'd)**

o: All medications (including prescription, non-prescription and supplements) for treatment of UC taken within 6 months prior to Screening; any other medication taken 1 month prior to Screening; and any concomitant medications (including tracking probiotic usage) during the study must be recorded. For all biologic treatments, the reason for discontinuation should be recorded at Screening.

p: All subjects are required to remain at the investigative site to be carefully monitored after each infusion for potential infusion reactions or other adverse events. Post-infusion safety monitoring is as follows:

Week 0 (Day 1 Baseline): minimum of 3 hours post-infusion at site and a phone call at approximately 48 to 72 hours post-infusion for any subject who does not return for the scheduled visit at the investigative site;

Week 2: minimum of 3 hours post-infusion at site and a phone call at approximately 48 to 72 hours post-infusion for any subject who does not return for a visit at the investigative site;

Weeks 4, 6, 8 and 10: minimum of 1 hour post-infusion at site.

CBC=complete blood count; ECG=electrocardiogram; eCRF=electronic case report form; FSH=follicle-stimulating hormone; HEENT=head, eyes, ears, nose, and throat; HIV=human immunodeficiency virus; IBDQ=Inflammatory Bowel Disease Questionnaire; LTE=long-term extension; mMES=modified Mayo endoscopy subscore; OLE=open-label extension; PK=pharmacokinetic(s); PPD=purified protein derivative; TB=tuberculosis; UC=ulcerative colitis; UCEIS=Ulcerative Colitis Endoscopic Index of Severity; US=United States; wr-CRP=wide-range C-reactive protein.

**Table 9-2 Study Schedule of Events - Open-label/Long-term Extension Maintenance Therapy and Follow-up Period**

Procedure	Treatment Period - OLE/LTE Therapy: Week 12 (First Dose) to Week 52 <sup>a</sup>											OLE/LTE Therapy Post-treatment Follow-up Period			
	Week 12											End-of-OLE/LTE Therapy	Follow-up 1	Follow-up 2	Follow-up 3
		Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Week 52 ± 7 days	Week 56 ± 7 days	Week 60 ± 7 days	End-of-Study Week 64 ± 7 days	
Inclusion/Exclusion Criteria <sup>b</sup>	X														
Physical Examination <sup>c</sup>	X										X				
Brief Physical Examination <sup>d</sup>		X	X	X	X	X	X	X	X	X		X	X	X	
Vital Signs <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X <sup>f</sup>	X <sup>f</sup>									X				
Hematology (CBC with diff & platelets)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry Profile	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Profile	X										X				
Multiplex-31 Assay	X										X				
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy <sup>g</sup>											X				
Urine Pregnancy <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool Enteric Pathogens (including <i>Clostridium difficile</i> )	X										X				
Partial Mayo Clinic Score (without sigmoidoscopy, includes review of diary) with Physician's Global Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

**Table 9-2 Study Schedule of Events - Open-label/Long-term Extension Maintenance Therapy and Follow-up Period**

Procedure	Treatment Period - OLE/LTE Therapy: Week 12 (First Dose) to Week 52 <sup>a</sup>											OLE/LTE Therapy Post-treatment Follow-up Period			
	Week 12											End-of-OLE/LTE Therapy	Follow-up 1	Follow-up 2	Follow-up 3
		Week 16 ± 7 days	Week 20 ± 7 days	Week 24 ± 7 days	Week 28 ± 7 days	Week 32 ± 7 days	Week 36 ± 7 days	Week 40 ± 7 days	Week 44 ± 7 days	Week 48 ± 7 days	Week 52 ± 7 days	Week 56 ± 7 days	Week 60 ± 7 days	End-of-Study Week 64 ± 7 days	
Flexible Sigmoidoscopy with biopsy for mMES, UCEIS, modified Baron score & total Mayo Clinic score (includes review of diary)	X (recommend 7 to 13 days prior to Week 12)										X <sup>h</sup> (at visit or within 21 days prior to Week 52)				
IBDQ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fecal Calprotectin <sup>i</sup>	X										X				
wr-CRP Assay	X			X			X				X			X	
Pharmacokinetics	For PK Sample Collection Schedule Refer to Table 10.4.1-1 for Cohorts 1 - 3 during Induction Therapy (Part A) and OLE/LTE and Table 10.4.1-2 for Cohort 4 during Induction Therapy (Part B) and OLE/LTE														
Anti-KHK4083 Antibodies <sup>j</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Flow Cytometry	Refer to Table 10.4.1-1 for Cohorts 1 - 3 and Table 10.4.1-2 for Cohort 4														
Future Biomarker Analyses (whole blood) <sup>k</sup>	X										X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product Administration <sup>a</sup> <b>On-site Post-infusion Monitoring Required<sup>m</sup></b>	X	X	X	X	X	X	X	X	X	X					

**Footnotes to Table 9-2**

- a: The OLE Therapy Dosing Regimen: 10 KHK4083 treatments to be administered as one IV infusion every 4 weeks (Weeks 12 to 48) at the dose administered to the subjects in the cohort (or a lower dose if that cohort is discontinued) during Induction Therapy. LTE Therapy Dosing Regimen: 10 additional KHK4083 or placebo treatments to be administered as one IV infusion every 4 weeks (Weeks 12 to 48) at the dose administered to the subjects in the cohort (or a lower dose if that cohort is discontinued) during Induction Therapy. Subjects in LTE who transition to the OLE should have visits and assessments as described in Section 6.1.4.
- b: Subjects who complete double-blind Induction Therapy must meet additional eligibility criteria (refer to Section 7.4) to receive OLE Therapy once every 4 weeks (first dose at Week 12) with a post-treatment Follow-up Period for 16 weeks after the subject's last infusion. The treatment at Week 12 will be administered at the scheduled visit or within 7 days after Week 12. 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 (refer to Section 6.1.4).
- c: Complete physical examinations include general appearance and examination of the HEENT and body systems (cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, and skin).
- d: Brief physical examinations only include the HEENT, cardiovascular, respiratory, and abdominal examinations.
- e: Vital signs include systolic and diastolic blood pressure, radial pulse, respiration rate, and oral body temperature.
- f: Perform ECG predose and at the end of infusion. Subjects who transition from LTE to OLE must have ECGs performed predose and at the end of infusion for the first two infusions.
- g: Female subjects considered to be women of childbearing potential must have a negative pregnancy test at Screening and Baseline. Subjects are considered to not be of childbearing potential if they are  $\geq 50$  years of age and without menses for 24 consecutive months; have a follicle-stimulating hormone level  $> 25$  mIU/mL (or in postmenopausal range per local laboratory standards); or have undergone a hysterectomy and/or a bilateral salpingo-oophorectomy.
- h: If the subject discontinues more than 8 weeks after the Week 12 visit, a sigmoidoscopy must be performed at End-of-Treatment. The sigmoidoscopy may be performed up to 4 weeks after the last dose of study medication.
- i: Fecal calprotectin concentration, which is usually elevated in subjects with moderately active UC, will be measured.
- j: Samples for anti-KHK4083 antibodies must be taken prior to dosing and taken at the same time as pre-dose PK samples shown in the Table 10.4.1-1 and Table 10.4.1-2.
- k: Whole blood will be collected and stored (frozen) for potential exploratory biomarker analyses in the future at Week 52 (End-of-OLE/LTE Therapy) and at the OLE/LTE Therapy Post-treatment Follow-up 3 visit.
- l: Record concomitant medications during the study and probiotic usage.
- m: All subjects are required to remain at the investigative site to be carefully monitored after each infusion for potential infusion reactions or other adverse events. Post-infusion safety monitoring is as follows:
  - Week 12 (first dose in OLE Therapy) or first dose in subjects who transition from LTE to OLE: minimum of 3 hours post-infusion at site and a phone call at approximately 48 to 72 hours post-infusion for any subject who does not return for a visit at the investigative site;
  - Week 16 (second dose in OLE Therapy) or second dose in subjects who transition from LTE to OLE : minimum of 3 hours post-infusion at site and a phone call at approximately 48 to 72 hours post-infusion for any subject who does not return for a visit at the investigative site;
  - All other doses in OLE after the first 2 doses: minimum of 1 hour post-infusion at site.

CBC=complete blood count; ECG=electrocardiogram; HEENT=head, eyes, ears, nose, and throat; IBDQ=Inflammatory Bowel Disease Questionnaire; IV=intravenous; LTE=long-term extension; mMES=modified Mayo endoscopy subscore; OLE=open-label extension; PK=pharmacokinetic(s); UC=ulcerative colitis; UCEIS=Ulcerative Colitis Endoscopic Index of Severity; wr-CRP=wide-range C-reactive protein.

## 9.1 Screening Period (Day –28 to Day –1)

At the Screening visit, the Investigator will review the ICF with each subject to ensure that the subject understands the study and the study procedures. The subject will read, sign, and date the ICF and other locally applicable documents. Screening evaluations used to determine the subject's study eligibility must be completed within the Screening Period (Day –28 to Day –1) prior to starting treatment on Day 1 (Week 0), and include a baseline sigmoidoscopy with biopsy being completed within 7 to 28 days prior to Day 1. For subjects who are rescreened, the original screening sigmoidoscopy can be used to satisfy the entry criteria if obtained within 42 days prior to the first dose. All sigmoidoscopy procedures will be performed using a flexible sigmoidoscope. Biopsies will be collected during the sigmoidoscopy procedure and tissue samples will be examined at a central laboratory. Immunohistochemical staining will be performed on all biopsy samples (refer to Section 10.4.1). Sigmoidoscopy scores will be determined by a central reader. The sigmoidoscopy results from the central reader are required before a subject is randomized in the study.

Subjects will be instructed on how to appropriately complete a daily diary to document symptoms of UC including stool frequency, rectal bleeding, abdominal discomfort, and general sense of well-being. Symptoms of UC must be recorded throughout the Screening Period. Diary entries will be reviewed by site personnel at all visits.

All subjects must satisfy all the Inclusion Criteria and none of the Exclusion Criteria listed in Sections 7.2 and 7.3, respectively.

A subject who was considered a Screen failure and not dosed with the investigational product is permitted to be re-screened once due to failure to meet the Inclusion/Exclusion Criteria, whereas subjects with other reasons for lack of randomization may be re-screened twice.

The following additional assessments will be performed during the Screening Period (Day –28 to Day –1) (refer to Table 9-1 for the schedule of study events at Screening):

- Main diagnosis - moderately active UC, severity of UC, duration of UC (sigmoidoscopy scores will be determined by a central reader);
- Demographics - age at Screening, sex, race, and ethnicity identifications;
- Medical and Surgical History - including concurrent illnesses; chest x-ray if needed (within previous 3 months) results, vaccinations (within previous 6 months), previous surgery for UC or other major or abdominal surgery, and anticipated requirement for surgery for UC or other major surgery;
- Childbearing potential;
- Complete physical examination (Section 10.6.4);

- Vital Signs (systolic and diastolic blood pressure, radial pulse, and respiration rate) and body temperature (oral) (Section 10.6.2);
- Body weight and height (Section 10.6.4);
- 12-lead ECG (Section 10.6.3);
- Previous treatment with corticosteroids, immunosuppressive medications or TNF antagonist therapy, any prior biologic treatment (e.g., infliximab, adalimumab, or golimumab), and prior investigational products or therapies (Section 8.5);
- Prior and concurrent prescriptions and non-prescription medications, including any other UC treatments such as probiotics and other over-the-counter medications and supplements. Stable doses of aminosalicylates, oral glucocorticoids, azathioprine, and 6-mercaptopurine are permitted as described in Section 8.5 (refer to Section 8.5.1 for prohibited medications);
- Tobacco use, alcohol use, active marijuana (medicinal or recreational) use, illicit substance use;
- Allergies/hypersensitivities;
- Diet special for UC;
- Pre-treatment AEs (Section 10.6.5);
- Clinical Laboratory Evaluations (Table 9-1; refer to Section 10.6.1 for list of tests): Blood samples will be drawn at Screening for serum chemistry, hematology, coagulation profile, serum pregnancy, hepatitis B and C, and HIV testing; TB screening will be performed using a PPD skin test or IGRA; urine samples will be collected for analysis and urine drug screen; and fecal samples will be collected (before the start of the preparations required for the sigmoidoscopy or as specified in the stool collection instruction section of the laboratory manual) for analysis, i.e., cultures for enteric pathogens, ova and parasite evaluation, and *Clostridium difficile* assay.
- Delayed-type hypersensitivity skin test with the *Candida albicans* antigen - at all investigative sites in the US and in other selected countries (Section 10.4.1). The skin testing site will be read within 48 to 72 hours following intradermal injection of the antigen. The largest diameter of induration will be measured in mm and recorded.

Total and partial Mayo scores for inclusion criteria will be determined based upon the Diary entries and Physician's Global Assessment at the Baseline Visit.

## **9.2 Baseline Visit (Week 0, Day 1)**

Before administration of KHK4083 or placebo, the subject's eligibility criteria (Inclusion/Exclusion Criteria) and results of Screening assessments must be reviewed by the Investigator (his/her designee) to ensure that the subject is qualified to be randomized in the study. A partial Mayo Clinic score (without sigmoidoscopy) including the Physician's Global Assessment, which is to be performed after review of all available clinical data, will be recorded at Baseline. A total Mayo clinical score will be evaluated at Baseline, using subject

diary entries within the 10 days prior to Baseline, combined with the sigmoidoscopy results prior to Baseline and the Physician's Global Assessment. Diary entries for the three qualifying days closest to Baseline will be used for this evaluation but the entries do not have to be made on consecutive days. A total Mayo score of 4-10 and endoscopy subscore (mMES determined by a central reader) of at least 2 are required as per the Inclusion Criteria (refer to Inclusion Criteria #5)

The sigmoidoscopy results from the central reader are required before a subject is randomized in the study (*Note: A sigmoidoscopy with biopsy, for mMES, UCEIS, modified Baron score and total Mayo Clinic score, is to be performed before randomization and within 7 to 28 days prior to the first dose; an mMES of at least 2 is required. For subjects who are rescreened, the original screening sigmoidoscopy can be used to satisfy the entry criteria if obtained within 42 days prior to the first dose.*)

An IBDQ will be administered as a quality-of-life assessment at Baseline.

The following will be collected at Baseline (Day 1) (refer to Table 9-1 for the schedule of study events at Baseline).

- Complete physical examination (Section 10.6.4);
- Vital signs (systolic and diastolic blood pressure, radial pulse, and respiration rate) and body temperature (oral) (Section 10.6.2);
- Body weight (Section 10.6.4);
- 12-lead ECG (Section 10.6.3);
- Adverse events (pre-treatment and on-site post-infusion monitoring is required for at least 3 hours after the first dose as well as a phone call at approximately 48 to 72 hours post-infusion for any subject who does not return for the scheduled visit at the investigative site) (Section 10.6.5);
- Concomitant medications (Section 8.5);
- Clinical laboratory evaluations (refer to Section 10.6.1 for list of tests): Blood samples will be collected at Baseline for serum chemistry, hematology, coagulation profile, and the multiplex-31 assay; a urine sample for urinalysis; and fecal sample (collect as specified in the stool collection instruction section of the laboratory manual) for PD assessment only;
- PK sampling at pre-dose and post-dose timepoints (refer to Table 10.4.1-1 and Table 10.4.1-2 for schedule of times for sample collection);
- PD assessments including fecal calprotectin, wide-range C-reactive protein (wr-CRP), and flow cytometry (refer to Table 10.4.1-1 and Table 10.4.1-2 for schedule of sample times);
- Immunogenicity assessment - serum samples at pre-dose timepoints (Section 10.4.2);

- Other potential study assessments - whole blood samples for future biomarker analyses (Section 10.4.3).

### **9.3 Double-blind Treatment Period (Induction Therapy and Long-term Extension Therapy) and Open-label Extension Therapy**

The double-blind Treatment Period comprises a 12-week Induction Therapy phase (Part A: Cohorts 1 - 3, multiple ascending doses; Part B: Cohort 4, recommended dose) followed by a 40-week OLE/LTE Therapy phase. Subjects in Part A are not allowed to participate in Part B.

A sigmoidoscopy with biopsy for mMES, UCEIS, modified Baron score and total Mayo Clinic score will be performed at Week 12 (i.e., it is highly recommended to perform the procedure 7 to 13 days prior to the Week 12 visit), and at the Week 52 visit or within 21 days prior to Week 52. The mMES will be determined by a central reader at Weeks 12 and 52. The sigmoidoscopy results from the central reader are required before a subject receives treatment in the OLE/LTE Therapy phase at Week 12. A total Mayo Clinic score will also be evaluated at Weeks 12 (prior to OLE/LTE dosing) and 52, using subject diary entries within the 7 days prior to each visit and sigmoidoscopy results prior to each visit. Since the preparations for the sigmoidoscopy can interfere with the assessment of other clinical parameters, the Mayo Clinic score should not include diary entries recorded on the day prior to, the day of, or the day after the sigmoidoscopy. A partial Mayo Clinic score (without sigmoidoscopy) including the Physician's Global Assessment, which is to be performed after review of all available clinical data, and the results from the IBDQ will be recorded at each visit during the Treatment Period. Mayo Clinic subscores will be derived from the diaries over the 2 to 3 qualifying days that are closest to each visit.

In addition, the following will be collected during the Treatment Period according to the schedule of study events in Table 9-1 (Induction Therapy) and Table 9-2 (OLE/LTE Maintenance Therapy):

- Brief physical examination (Section 10.6.4);
- Vital signs (systolic and diastolic blood pressure, radial pulse, and respiration rate) and body temperature (oral) (Section 10.6.2);
- Body weight (Section 10.6.4);
- 12-lead ECG (Section 10.6.3);
- Adverse events -
  - On-site post-infusion monitoring is required for at least 3 hours after the first 2 double-blind infusions (Weeks 0 and 2) are completed for each subject and for at least

- 1 hour after all other double-blind infusions (Weeks 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48).
- On-site post-infusion monitoring is required for at least 3 hours after the first 2 open-label infusions (Weeks 12 and 16) are completed for each subject and for at least 1 hour after all other open-label infusions (Weeks 20, 24, 28, 32, 36, 40, 44, and 48)  
Note: Some subjects in the LTE may transition to the OLE after Week 12 and up to Week 28. Post-infusion monitoring is required for at least 3 hours after the first 2 open-label infusions.
  - In addition, a phone call to each subject will be conducted at approximately 48 to 72 hours following the completion of the first and second infusions (double-blind and open-label) for any subject who does not return for a visit at the investigative site (Section 10.6.5);
- Concomitant medications (Section 8.5);
  - Clinical laboratory evaluations (refer to Section 10.6.1 for list of tests): Blood samples will be collected at specified times for serum chemistry, hematology, coagulation profile, and the multiplex-31 assay; urine samples for urinalysis; and fecal samples (collect before the start of the preparations required for the sigmoidoscopy or as specified in the stool collection instruction of the laboratory manual) for PD assessments as described below and for cultures for enteric pathogens, ova and parasite evaluations, and *Clostridium difficile* assays at Weeks 12 and 52;
  - PK sampling at pre-dose and post-dose timepoints (refer to Table 10.4.1-1 and Table 10.4.1-2 for schedule of days/times for sample collection);
  - PD assessments including fecal calprotectin, wr-CRP, delayed-type hypersensitivity testing, and flow cytometry (refer to Table 10.4.1-1 and Table 10.4.1-2 for schedule of sample times). The delayed-type hypersensitivity skin testing site will be read within 48 to 72 hours following intradermal injection of the *Candida albicans* antigen at Week 10. The largest diameter of induration will be measured in mm and recorded;
  - Immunogenicity assessment - serum samples at pre-dose or time of visit timepoints (Section 10.4.2);
  - Other potential study assessments - whole blood samples will be collected for future biomarker analyses (Section 10.4.3).

#### **9.4 Post-treatment Follow-up Period**

A safety Post-treatment Follow-up Period will continue for 16 weeks after the last infusion associated with the subject's treatment period and will include 3 Post-treatment Follow-up visits. For subjects who only receive Induction Therapy (i.e., do not continue in OLE/LTE Therapy), the Post-treatment Follow-up visits will be at Weeks 16, 20, and 26. For all subjects who receive both Induction Therapy and OLE/LTE Therapy, the post-treatment follow-up visits will be at Weeks 56, 60, and 64. A partial Mayo Clinic score (without sigmoidoscopy) including the Physician's Global Assessment, which is to be performed after

review of all available clinical data, and the results from the IBDQ will be recorded at each visit during the Treatment Period. Subjects removed from the study for AEs will be followed until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved. Safety measurements will be performed from KHK4083 (or placebo) administration until the final safety follow-up assessment. In addition, the following will be collected during the Post-treatment Follow-up Period according to the schedule of study events in Table 9-1 (Induction Therapy) and Table 9-2 (OLE/LTE Maintenance Therapy):

- Brief physical examination (Section 10.6.4);
- Vital signs (systolic and diastolic blood pressure, radial pulse, and respiration rate) and body temperature (oral) (Section 10.6.2);
- Body weight (Section 10.6.4);
- Adverse events (Section 10.6.5);
- Concomitant medications (Section 8.5);
- Clinical laboratory evaluations (refer to Section 10.6.1 for list of tests): Blood samples will be collected at specified times for serum chemistry, hematology, and the multiplex-31 assays (i.e., if the subject does not continue in OLE Therapy); urine samples will be collected for urinalysis;
- PK sampling at the time of the follow-up visits (refer to Table 10.4.1-1 and Table 10.4.1-2 for schedule of days/times for sample collection);
- PD assessment - wr-CRP testing at follow-up visit (Week 26 or Week 64);
- Immunogenicity assessment - serum samples at the time of the follow-up visits (Section 10.4.2).

## **10 EFFICACY, PHARMACOKINETIC, PHARMACODYNAMIC, IMMUNOGENICITY, SAFETY, AND OTHER VARIABLES**

The efficacy variables include mMES, UCEIS score, modified Baron endoscopic score, total Mayo Clinic score, partial Mayo Clinic score (without sigmoidoscopy), and an IBDQ score.

The PK variables include the maximum observed serum concentration ( $C_{max}$ ); time of maximum observed serum concentration ( $t_{max}$ ), trough concentration at the end of the dosing interval ( $C_{min}$ ), area under the serum concentration-time curve ( $AUC_{0-t}$ ,  $AUC_{0-\tau}$ ,  $AUC_{0-\infty}$ ), terminal elimination half-life ( $t_{1/2}$ ), systemic serum clearance (CLs), volume of distribution at steady state ( $V_{ss}$ ), volume of distribution at terminal phase ( $V_z$ ), and accumulation ratio ( $R_{ac}$ ).

The PD variables include the measurement of fecal calprotectin, and C-reactive protein concentrations (using wr-CRP assay, see Central Laboratory Manual for details). Other PD assessments include delayed-type hypersensitivity skin testing with the *Candida albicans* antigen (at all investigative sites in the US and in other selected countries),

immunohistochemical staining for OX40 or other immune-related antigens on all endoscopic biopsy samples, and flow cytometry analyses on whole blood or PBMCs for the measurement of specific immune-related cells.

For immunogenicity, the development of anti-KHK4083 antibodies will be assessed.

The safety variables include AEs, SAEs, physical examinations, vital signs, body weight, 12-lead ECGs, and clinical laboratory evaluations (serum chemistry, hematology, coagulation profile, and urinalysis). Details of the safety assessments are provided in Section 10.6.

## **10.1 Primary Endpoints**

### **10.1.1 Efficacy**

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.

### **10.1.2 Safety**

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.

## **10.2 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 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  $\leq 2$  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. The PK for KHK4083 will be characterized in the UC subject population following multiple ascending doses.

### **10.3 Exploratory Endpoints**

Efficacy and PD exploratory endpoints will be included in this study for all subjects with moderately active UC who receive both Induction Therapy and OLE/LTE Maintenance Therapy. The exploratory endpoints for all subjects who receive both Induction Therapy and OLE/LTE Maintenance 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  $\leq 2$  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);
- PD profile of KHK4083;
- PK-PD relationships.

## **10.4 Pharmacokinetic, Pharmacodynamic, Immunogenicity and Other Study Assessments**

### **10.4.1 Pharmacokinetic and Pharmacodynamic Assessments**

#### **Pharmacokinetics:**

Blood samples for the measurement of KHK4083 in serum will be collected from all subjects in this study. The serum KHK4083 concentration data will be used to evaluate the PK of KHK4083.

#### **Pharmacodynamic Assessments:**

The PD assessments include fecal calprotectin at Weeks 0 (Baseline), 2, 12 (End-of-Induction Therapy visit), and 52 (End-of-OLE/LTE Therapy visit); and wr-CRP assays at Week 0 (Baseline), all visits during Induction Therapy, at Induction Therapy Follow-up Visit 3 (Week 26 only for subjects not continuing to OLE/LTE Therapy), during OLE/LTE Therapy

at Weeks 24, 36, and 52, and at OLE/LTE Therapy Follow-up Visit 3 (Week 64). Refer to Table 9-1 and Table 9-2 assessments at each therapy phase of the Treatment Period.

Delayed-type hypersensitivity skin testing with the *Candida albicans* antigen will be performed at Screening and Week 10 of Induction Therapy at all investigative sites in the US and in other selected countries.

Immunohistochemical staining will be performed on all biopsy samples obtained through sigmoidoscopy (Baseline [Week 0], Week 12, and Week 52).

Flow cytometry analyses will be performed on whole blood or PBMCs for the measurement of specific immune-related cells. The samples will be collected at Week 0 (Days 1, 2, and 8), during Induction Therapy (Weeks 2, 4, and 6), Week 12 (End-of-Induction Therapy visit), and at Week 52 (End-of-OLE/LTE Therapy visit) (refer to Section 10.4.1.1 for specific collection times). Additional whole blood samples may be collected as needed if a subject experiences a flare-up during OLE/LTE Therapy.

#### **10.4.1.1 Sampling Times and Assays for Pharmacokinetics and Pharmacodynamics (Flow Cytometry)**

Serum samples for PK and PD will be collected from subjects in Cohorts 1 - 3 during Induction Therapy (Part A) and OLE/LTE Therapy according to the schedule in Table 10.4.1-1 and subjects in Cohort 4 during Induction Therapy (Part B) and OLE/LTE Therapy according to the schedule in Table 10.4.1-2.

**Table 10.4.1-1 Cohorts 1 - 3: Sample Collection Schedule During Induction Therapy (Part A), Long-term Extension, and Open-label Extension Therapy for Pharmacokinetics and Pharmacodynamics (Flow Cytometry)**

Visit (Days within Scheduled Visit)	Day	Time	PK	PD (FCM)
<b>Double-blind Induction Therapy (Part A)</b>				
Week 0	1	Before Administration	X	X
		End of Infusion	X	
		4 hours $\pm$ 15 min from Start of Infusion	X	
	2	At the time of visit	X	X <sup>a</sup>
	8 ( $\pm$ 1 day)	At the time of visit	X	X <sup>a</sup>
Week 2 ( $\pm$ 2 days)	1 <sup>b</sup>	Before administration	X	X
Week 4 ( $\pm$ 4 days)	1	Before administration	X	X
Week 6 ( $\pm$ 4 days)	1	Before administration	X	X
Week 8 ( $\pm$ 4 days)	1	Before administration	X	
Week 10 ( $\pm$ 4 days)	1	Before administration	X	
		End of Infusion	X	
		4 hours $\pm$ 15 min from Start of Infusion	X	
	2	At the time of visit	X	
	8 ( $\pm$ 1 day)	At the time of visit	X	
End-of-Treatment Week 12 ( $\pm$ 4 days)	1 <sup>c</sup>	At the End-of-Induction Therapy visit	X	X
Week 16 ( $\pm$ 7 days) Follow-up 1	1 <sup>d</sup>	At the time of visit	X	
Week 20 ( $\pm$ 7 days) Follow-up 2	1 <sup>d</sup>	At the time of visit	X	
Week 26 ( $\pm$ 7 days) Follow-up 3	1 <sup>d</sup>	At the time of visit	X	
<b>Double-blind Long-term Extension Therapy or Open Label Extension<sup>e</sup></b>				
Week 12 ( $\pm$ 4 days)	1 <sup>c</sup>	Before administration	X	
Week 16 ( $\pm$ 7 days)	1	Before administration	X	
Week 20 ( $\pm$ 7 days)	1	Before administration	X	
Week 24 ( $\pm$ 7 days)	1	Before administration	X	
Week 28 ( $\pm$ 7 days)	1	Before administration	X	
Week 32 ( $\pm$ 7 days)	1	Before administration	X	
Week 36 ( $\pm$ 7 days)	1	Before administration	X	
Week 40 ( $\pm$ 7 days)	1	Before administration	X	
Week 44 ( $\pm$ 7 days)	1	Before administration	X	

**Table 10.4.1-1 Cohorts 1 - 3: Sample Collection Schedule During Induction Therapy (Part A), Long-term Extension, and Open-label Extension Therapy for Pharmacokinetics and Pharmacodynamics (Flow Cytometry)**

Visit (Days within Scheduled Visit)	Day	Time	PK	PD (FCM)
<b>Double-blind Long-term Extension Therapy or Open Label Extension(cont'd)</b>				
Week 48 ( $\pm 7$ days) <sup>f</sup>	1	Before administration	X	
		End of Infusion <sup>f</sup>	X	
		4 hours $\pm$ 15 min from Start of Infusion <sup>f</sup>	X	
	2	At the time of visit <sup>f</sup>	X	
	8 ( $\pm 1$ day)	At the time of visit <sup>f</sup>	X	
	15 ( $\pm 1$ day)	At the time of visit <sup>f</sup>	X	
	22 ( $\pm 1$ day)	At the time of visit <sup>f</sup>	X	
Week 52 ( $\pm 7$ days)	1 <sup>g</sup>	At the time of visit	X	X
Week 56 ( $\pm 7$ days) Follow-up 1	1	At the time of visit	X	
Week 60 ( $\pm 7$ days) Follow-up 2	1	At the time of visit	X	
Week 64 ( $\pm 7$ days) Follow-up 3 End-of-Study	1	At the time of visit	X	

a: Hematology parameters will also be assessed.

b: Sample will be considered a Day 15 post-dose sample for Week 0 and a pre-dose sample for Week 2.

c: For subjects who do not continue OLE/LTE Therapy, this sample will be Day 15 post-dose sample for Week 10; for subjects who continue the OLE/LTE Therapy, this sample will be a pre-dose sample at Week 12.

d: Sample will be collected only if the subject enters the Induction Therapy Post-treatment Follow-up Period and is not continuing to OLE/LTE Therapy.

e: If a subject experiences a flare-up during OLE/LTE Therapy whole blood samples may be collected.

f: All post-infusion samples may be collected at Week 44 instead of the Week 48 visit.

g: Sample will be considered Day 28 post-dose for Week 48.

FCM=flow cytometry; LTE=long-term extension; OLE=open-label extension; PD=pharmacodynamics;

PK=pharmacokinetics.

**Table 10.4.1-2 Cohort 4: Sample Collection Schedule During Induction Therapy (Part B) and Long-term Extension Therapy and Open Label Extension Therapy for Pharmacokinetics and Pharmacodynamics (Flow Cytometry)**

Visit (Days within Scheduled Visit)	Day	Time	PK	PD (FCM)
<b>Double-blind Induction Therapy (Part B)</b>				
Week 0	1	Before Administration	X	X
		End of Infusion	X	
Week 2 ( $\pm$ 2 days)	1 <sup>a</sup>	Before administration	X	X
Week 4 ( $\pm$ 4 days)	1	Before administration	X	X
Week 6 ( $\pm$ 4 days)	1	Before administration	X	X
Week 8 ( $\pm$ 4 days)	1	Before administration	X	
Week 10 ( $\pm$ 4 days)	1	Before administration	X	
		End of Infusion	X	
End-of-Treatment/ Week 12 ( $\pm$ 4 days)	1 <sup>b</sup>	At the End-of-Induction Therapy visit	X	X
Week 16 ( $\pm$ 7 days) Follow-up 1	1 <sup>c</sup>	At the time of visit	X	
Week 20 ( $\pm$ 7 days) Follow-up 2	1 <sup>c</sup>	At the time of visit	X	
Week 26 ( $\pm$ 7 days) Follow-up 3	1 <sup>c</sup>	At the time of visit	X	
<b>Double-blind Long-term Extension Therapy or Open Label Extension Therapy<sup>d</sup></b>				
Week 12 ( $\pm$ 4 days)	1 <sup>b</sup>	Before administration	X	
Week 16 ( $\pm$ 7 days)	1	Before administration	X	
Week 20 ( $\pm$ 7 days)	1	Before administration	X	
Week 24 ( $\pm$ 7 days)	1	Before administration	X	
Week 28 ( $\pm$ 7 days)	1	Before administration	X	
Week 32 ( $\pm$ 7 days)	1	Before administration	X	
Week 36 ( $\pm$ 7 days)	1	Before administration	X	
Week 40 ( $\pm$ 7 days)	1	Before administration	X	
Week 44 ( $\pm$ 7 days)	1	Before administration	X	
Week 48 ( $\pm$ 7 days)	1	Before administration	X	
End-of-Treatment/ Week 52 ( $\pm$ 7 days)	1 <sup>c</sup>	At the time of visit	X	X
Week 56 ( $\pm$ 7 days) Follow-up 1	1	At the time of visit	X	
Week 60 ( $\pm$ 7 days) Follow-up 2	1	At the time of visit	X	
Week 64 ( $\pm$ 7 days) Follow-up 3 End-of-Study	1	At the time of visit	X	

**Footnotes to Table 10.4.1-2.**

- a: Sample will be considered a Day 15 post-dose sample for Week 0 and a pre-dose sample for Week 2.
- b: For subjects who do not continue OLE/LTE Therapy, this sample will be Day 15 post-dose sample for Week 10; for subjects who continue the OLE/LTE Therapy, this sample will be a pre-dose sample at Week 12.
- c: Sample will be collected only if the subject enters the Induction Therapy Post-treatment Follow-up Period and is not continuing to LTE Therapy.
- d: If a subject experiences a flare-up during OLE/LTE Therapy collect whole blood and FCM.
- e: Sample will be considered Day 28 post-dose for Week 48.

FCM=flow cytometry; LTE=long-term extension; OLE=open-label extension; PD=pharmacodynamics;

PK=pharmacokinetics

### **10.4.1.2 Sample Collection, Preparation, Labeling, and Storage**

All PK samples must be shipped to the designated central laboratory for storage and batches of samples will be shipped to the analytical testing laboratory. Details of the collection, storage, handling, and shipping of all samples are provided in the Central Laboratory Manual sent to investigative sites prior to the study initiation visit.

### **10.4.2 Immunogenicity Assessments**

Immunogenicity assessments for detection of antibodies against KHK4083 will be evaluated from samples collected from all subjects during the study.

Serum samples will be collected before the initial dose of investigational product at specified collection time windows at Week 0 (Baseline, Day 1) and at all visit weeks during Induction Therapy (pre-dose at Weeks 2, 4, 6, 8, and 10); at the End-of-Induction Therapy visit (only for subjects not continuing to OLE/LTE Therapy); during the Induction Therapy Follow-up Period (only for subjects not continuing to OLE/LTE Therapy) visits (Weeks 16, 20, and 26); during OLE/LTE Therapy (pre-dose at Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48); at the End-of-OLE/LTE Therapy visit (Week 52); and during the OLE/LTE Therapy Follow-up Period visits (Weeks 56, 60, and 64) as described in the visit schedule for sample collection in Table 9-1 and Table 9-2.

Details of the collection, storage, handling, and shipping of all samples are provided in the Central Laboratory Manual that will be sent to investigative sites prior to the study initiation visit.

### **10.4.3 Other Potential Study Assessments**

For future exploratory biomarker analyses, whole blood samples will be collected as described in the visit schedule for sample collection in Table 9-1 and Table 9-2. All samples

will be labeled and maintained in frozen storage conditions according to the instructions provided in the Central Laboratory Manual.

### **10.5 Medical/Surgical History, Medication History, and Demographics**

Subject demographics (race, ethnicity, sex, and age), medical history including vaccinations (within previous 6 months), current medical conditions, diagnosed chronic conditions, and conditions resolved within the past year will be recorded in detail at the Screening visit. The subject's surgical history particularly previous surgery for UC or other major or abdominal surgery, and anticipated requirement for surgery for UC or other major surgery will also be recorded at the Screening visit (refer to Section 9.1).

Any prior biologic treatment or prior investigational products or therapies including the reason for discontinuation of treatment and all medications for treatment of UC taken within 6 months prior to Screening; and any other previous medication taken 1 month prior to Screening will be documented in detail. Refer to products listed in Inclusion Criteria (Section 7.2) and Exclusion Criteria (Section 7.3); and to Section 8.5 and Section 8.5.1 (prohibited medications) for additional medication details during the Screening and Treatment Period.

Additional background information will be recorded at Screening including tobacco, alcohol, active marijuana (medicinal or recreational), and illicit substance use; allergies/hypersensitivities; and probiotic use and special diet for UC.

### **10.6 Safety Assessments**

All subjects will be assessed regularly for potential occurrence of AEs from the time of signing the ICF until 16 weeks after the last dose of investigational product or any time thereafter if a causal relationship is suspected.

The following information will be collected to evaluate the safety profile of the study population:

- Clinical laboratory evaluations (serum chemistry, hematology, coagulation profile, and urinalysis);
- Vital signs and body weight;
- 12-lead ECG;
- Physical examination; and
- Adverse events (including SAEs).

### **10.6.1 Clinical Laboratory Evaluation**

Clinical laboratory parameters assessed in this study are displayed in Table 10.6.1-1. The collection times for blood, urine, and fecal specimens during the study are specified in Table 9-1 and Table 9-2.

**Table 10.6.1-1 Clinical Laboratory Assessments**

<b>Serum Chemistry<sup>a</sup></b>	SGOT (AST) SGPT (ALT) Creatine kinase LDH Alkaline phosphatase Total bilirubin Folate Glucose	Creatinine Albumin BUN Sodium Potassium Calcium Vitamin B12	Chloride Total cholesterol Triglycerides Uric Acid Amylase Lipase
<b>wr-CRP Assay</b>	To be performed on serum chemistry samples at Week 0 (Baseline), all visits during Induction Therapy, Week 26 (only for subjects not continuing to OLE/LTE Therapy), and at Weeks 24, 36, 52, and 64.		
<b>Multiplex-31 Assay</b>	To be performed at Baseline (Week 0), Week 2, Week 12, and Week 52 or at a follow-up visit if the subject does not continue in OLE/LTE Therapy.		
<b>Diabetes Screening</b>	Subjects with glycated serum hemoglobin A1c $\geq$ 9% will be excluded from the study.		
<b>Coagulation Profile</b>	prothrombin time partial thromboplastin time		
<b>Hematology<sup>a</sup></b>	Hemoglobin Hematocrit RBCs	WBC count Differential and absolute counts Platelet count	
<b>Urinalysis</b>	Color Specific Gravity pH Protein Glucose Ketones	Bilirubin Urobilinogen Occult blood Nitrites Microscopic examination, if clinically indicated, including RBCs, WBCs, casts, bacteria and crystals	
<b>Urine Drug Screening</b>	Barbiturates, Benzodiazepines, Amphetamines, Cocaine, Cannabinoids, Opiates, Methamphetamine, Alcohol, and Cotinine		
<b>Serum FSH Test</b>	To be performed on all presumed post-menopausal females at Screening. Post-menopausal females are defined as females with the complete absence of menses for 24 consecutive months; have an FSH level $>$ 25 mIU/mL (or in postmenopausal range per local laboratory standards) in the absence of hormone replacement therapy.		
<b>Serum and/or Urine Pregnancy Test</b> (minimum sensitivity 25 IU/L or equivalent units of $\beta$ -HCG)	To be performed for all female subjects considered to be women of childbearing potential at Screening and at specified timepoints during the Treatment Period. <i>Note: Subjects are considered to not be of childbearing potential if they are <math>\geq</math> 50 years of age and without menses for 24 consecutive months and have an FSH level <math>&gt;</math> 25 mIU/mL (or in postmenopausal range per local laboratory standards); or have undergone a hysterectomy and/or a bilateral salpingo-oophorectomy.</i>		
<b>Hepatitis B and C, and HIV testing</b>	hepatitis B surface antigen or hepatitis B core antibody hepatitis C antibody (If positive, do reflex to RNA by RT-PCR testing) HIV-1 antibodies, HIV-1 antigen, HIV-2 antibody		

**Table 10.6.1-1 Clinical Laboratory Assessments**

<p><b>Tuberculosis Screening</b> using PPD Skin Test (by investigative site) and/or IGRA (clinical laboratory) (See details in Section 7.3, Exclusion Criterion 16)</p>	<p>Standard PPD skin test or IGRA (but not both) to be performed at Screening at investigative site. If positive (i.e., PPD measures &gt; 5 mm induration), follow up after Screening is required. An IGRA is to be performed at Screening if a subject has a history of positive PPD.</p> <p><i>Note: Performing of both IGRA and PPD tests in the same subject should be avoided as Screening procedures. Positivity of one of the tests cannot be voided by negativity of the other, i.e., subjects with positive PPD and negative IGRA test performed as a part of Screening will be considered TB positive and will be required to start prophylactic anti-TB therapy prior to infusion of investigational product according to local treatment standards. All safety laboratory tests may be repeated. Screening procedures may be extended by 2 weeks.</i></p>
<p><b>Delayed-Type Hypersensitivity Skin Test</b></p>	<p>At investigative sites in the US and other identified countries, the skin tests are to be performed at Screening and Week 10. The skin testing site will be read within 48 to 72 hours following intradermal injection of the <i>Candida albicans</i> antigen. The largest diameter of induration will be measured in mm and collected.</p>
<p><b>Fecal Sample Analysis</b></p>	<p>Stool cultures to identify enteric pathogens, ova and parasite evaluations, and <i>Clostridium difficile</i> assays are to be performed at Screening, Week 12, and Week 52. Refer to PD assessments for fecal calprotectin measurements at Baseline (Week 0) and Weeks 2, 12, and 52.</p>

a: A subject will be excluded from the study if a specific serum chemistry or hematology value at Screening is outside of the acceptable range as defined in Section 7.3, Exclusion Criteria.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; β-HCG=beta human chorionic gonadotrophin; ; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; IGRA=interferon gamma release assay; LDH=lactate dehydrogenase; LTE=long-term extension; OLE=open-label extension; PD=pharmacodynamic(s); PPD=purified protein derivative; RBC=red blood cell; RNA=ribonucleic acid; RT-PCR=Real-time reverse transcription-polymerase chain reaction; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TB=tuberculosis; US=United States; WBC=white blood cell; wr-CRP=wide-range C-reactive protein.

Any clinically important abnormal laboratory values noted at the Screening visit will be recorded as medical history. In addition, in order for the Sponsor to collect additional information about clinically important laboratory abnormalities, at minimum, the following laboratory abnormalities should be captured as appropriate:

- Any laboratory test result that meets the criteria for an SAE;
- Any laboratory abnormality that requires the subject to have study treatment discontinued or interrupted;
- Any laboratory abnormality that requires the subject to receive specific corrective therapy.

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until (1) the value returns to baseline, (2) the value is judged to be clinically acceptable by the Investigator and the Sponsor, or (3) a diagnosis that explains the

abnormal laboratory value is made. When possible, the Investigator should report the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin).

### **10.6.2 Vital Signs**

Vital signs and body temperature (measured orally) will be measured at Screening, all visits during the Treatment Period, and Follow-up Period visits. Vital signs, including systolic and diastolic blood pressure, radial pulse and respiration rate, will be measured after the subject has rested for at least 5 minutes in a supine or semi-supine position. Vital signs and body temperature will be monitored during IV infusion of the investigational product and periodically over the observation period after infusion. Additional vital sign measurements will be obtained at the discretion of the Investigator or designee if clinically significant signs or symptoms occur.

### **10.6.3 Electrocardiograms**

A standard 12-lead ECG will be performed at Screening; during Induction Therapy (pre-dose and at the end of infusion) on Day 1 (Baseline, Week 0), Week 8, and Week 10 (refer to Table 9-1); during OLE therapy on Week 12 (pre-dose and at the end of infusion), Week 16 (pre-dose and at the end of infusion) (refer to Table 9-2); and at Week 52 of OLE/LTE Therapy (refer to Table 9-2). Subjects who transition from LTE to OLE must have ECGs performed pre-dose and at the end of infusion for the first two infusions. The ECGs will be recorded after the subject has rested for approximately 5 minutes in a supine position. When PK collections and ECG recordings are scheduled at the same time point, the ECG recording should be prior to the PK sample collection.

#### **10.6.3.1 Investigative Site Responsibilities**

The Investigator is responsible for evaluating the ECG interpretation in relationship to clinical signs and symptoms and reaching a medical decision regarding the subject's medical status. The ECG findings should be assessed by the Investigator as normal, abnormal not clinically significant, or abnormal clinically significant, as appropriate. All abnormalities, whether assessed as clinically significant or not, will be recorded. The ECG tracing should be initialed and dated by the Investigator.

#### **10.6.3.2 ECG Core Laboratory Responsibilities**

The use of a central ECG laboratory or central reader may be requested on an adhoc basis.

## **10.6.4 Physical Examination**

The Investigator will perform complete physical examinations including general appearance and examination of head, eyes, ears, nose, and throat (HEENT) and body systems (cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, and skin) at Screening, Baseline (Week 0, Day 1), End-of-Induction Therapy (Week 12), and End-of-OLE/LTE Therapy (Week 52). Brief physical examinations (only include HEENT, cardiovascular, respiratory, and abdominal examinations) will be performed at all other visits during the Treatment Period and Follow-up Periods as specified in Table 9-1 and Table 9-2.

Body weight (kg) and height (cm) will be obtained while the subject is wearing light clothing (without shoes). Body weight will be documented during the Screening visit and at each study visit during the Treatment Period and Follow-up Period; height will be recorded at the Screening visit only (refer to Table 9-1 and Table 9-2)

## **10.6.5 Adverse Events**

### **10.6.5.1 Definitions**

An AE is defined as any untoward medical occurrence in a clinical study subject administered an investigational product and does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign (e.g., an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product whether or not considered related to the product.

An AE includes but is not limited to:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (i.e., a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (e.g., use for non-clinical reasons) of an investigational or marketed product.

The collection of AE and SAE information commences following the subject's written consent to participate in the study. The Investigator will inquire about AEs at all subject visits by asking the subject a non-leading question such as: "How have you been feeling since your last visit?" All AEs, whether observed by the Investigator or reported by the subject, must be collected. If a subject experiences an AE or SAE, the subject will receive appropriate treatment and supportive care as necessary, and the Investigator will continue to follow up

until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved.

In addition to the Investigator's own description of the AEs, each AE will be coded by the Sponsor according to the Medical Dictionary for Regulatory Activities (MedDRA).

#### **10.6.5.2 Assessment of Intensity**

All AEs will be classified either as mild, moderate, or severe in intensity as defined below:

- **Mild** – Event results in mild or transient discomfort, not requiring intervention, or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
- **Moderate** – Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
- **Severe** – Event results in significant symptoms that prevents normal daily activities; requires interventional treatment and may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

*Refer to Section 7.5.3 regarding withholding investigational product administration if the subject experiences a severe AE not related or of unclear relationship to the investigational product; and discontinuing investigational product administration if the subject experiences a severe AE related to the investigation product.*

The Investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the investigational product or not) until the outcome of the AE has been determined. The AE must be monitored until the return to the subject's baseline condition or until clinically satisfactory resolution is achieved (e.g., Grade 1 or stable).

#### **10.6.5.3 Assessment of Relationship**

The causal relationship of each AE to the investigational product (KHK4083 or placebo) must be determined by a medically qualified individual. The causal relationship should be assessed as one of the following:

##### **Related**

There is a reasonable causal relationship between the investigational product administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

##### **Not related**

There is not a reasonable causal relationship between the investigational product administration and the AE.

#### 10.6.5.4 Classifying Infusion Reactions

- **Mild** - infusion reaction requires no intervention and no interruption of the infusion; however, infusion interruption is permitted to observe the subject for resolution of any signs/symptoms before re-starting the infusion.
- **Moderate** - infusion reaction requires possible intervention (e.g., paracetamol orally and diphenhydramine 50 mg IV or an equivalent anti-histamine may be administered) and interruption of the infusion for at least 15 to 30 minutes prior to re-starting or discontinuing the infusion.
- **Severe** - infusion reaction requires medical intervention (i.e., immediate medical/nursing assessment and indicated supportive management per the institutional standard of care and local Investigator judgment until the signs/symptoms of the reaction have resolved) and immediate discontinuation of the infusion.

Refer to Section 8.1.3.3 for additional details on continuing or discontinuing investigational product administration following an acute infusion reaction.

#### 10.6.6 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is immediately life threatening. The term “life threatening” as part of the definition of “serious” refers to an event in which the subject was at imminent risk of death without urgent intervention at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.
- Is another important medical event. Important medical events are those that may not result in death, be life threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed above.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias that does not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on the outcome or action criteria usually associated with events that

pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

All AEs, whether non-serious or serious, must be recorded as appropriate. In addition, any AE that is initially considered serious or becomes serious must be reported as an SAE.

#### **10.6.6.1 Notification of Institutional Review Board or Independent Ethics Committee of Serious Adverse Events**

The Investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB or IEC. The IRB/IEC must be informed in a timely manner by the Investigator of SAEs occurring at their investigative site during the study. Investigators must also submit safety information provided by the Sponsor to the IRB. Investigators (or the Sponsor accordingly to specified regulations) also must submit safety information to the IEC.

#### **10.6.6.2 Adverse Event Contacts**

All SAE reports and follow-up SAE documentation should be emailed to the Sponsor's Drug Safety Surveillance Department: [SAESource@kyowa-kirin-pharma.com](mailto:SAESource@kyowa-kirin-pharma.com).

#### **10.6.6.3 Urgent Safety Measures**

In accordance with the principles of GCP as described in ICH E6, the Investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure, which an Investigator may need to implement, which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subject(s) without prior IRB/IEC approval/favorable opinion.

The Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazards to their health or safety. However, the **Investigator must inform the Sponsor within 24 hours of having taken such measures.**

All dose-limiting toxicity reports, non-emergency inquiries, and general information regarding this study should be directed to the Clinical Trial Manager, or Medical Monitor. All urgent safety measures meeting the criteria for an SAE must be reported to the Sponsor within 24 hours of taking safety measures. Such reports can be initiated by telephone but must be officially documented by the Investigator by email ([SAESource@kyowa-kirin-pharma.com](mailto:SAESource@kyowa-kirin-pharma.com)) and must include details of what measures were taken and the circumstances giving rise to those measures.

### **10.6.7 Adverse Event and Serious Adverse Event Reporting**

The description of each AE will identify the subject, date of onset, the date of resolution, the severity of the event, the action taken regarding the AE and the investigational product (KHK4083 or placebo), the outcome of the event, and the relationship of the event to KHK4083 or placebo. A medical condition present at Screening, but that has increased in frequency or severity, must be recorded as an AE. For screen failures, SAEs should be collected and recorded only until the subject is determined to be a screen failure. Screening or withdraws consent to participate in the study, except for SAEs that occur outside of that window which are attributed to screening-specific procedures. All AEs with onset after signing of the ICF should be collected. Adverse events which occur prior to first administration of investigational product should be identified as occurring pretreatment. No AE data should be entered on the eCRF for screen failures.

Standard medical terminology should be used to document AEs. The subject's exact description of the event will be recorded in the source documentation. In the case of signs and symptoms, the underlying illness or diagnosis will be recorded as the event when known. For SAEs, a single term for the diagnosis or underlying illness should be provided on the SAE Report form; if the underlying illness/diagnosis is unknown, the chief sign/symptom making the event serious should be recorded. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported according to regulatory guidelines.

All serious and non-serious AEs must be followed for a final outcome until the end of the Post-treatment Follow-up Period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

All SAEs require expeditious handling to comply with regulatory requirements. **Any SAE occurring in a clinical study subject must be reported to the Sponsor or designee within 24 hours of the Investigator having knowledge of the SAE.**

The Investigator or other qualified individual at the investigative site must complete the SAE Report form and e-mail it to the Sponsor or designee. All telephone communication regarding an SAE must be followed by a written report.

The Investigator is obligated to immediately report to the Sponsor or designee any SAE occurring at any time after the subject signs the ICF and within 16 weeks after the last dose of investigational product, independent of the circumstances or suspected cause. In addition, the Investigator must promptly report to the Sponsor any SAE occurring at any other time after

completion of the study if a causal relationship to KHK4083 is suspected. For all SAEs, the Investigator is obligated to pursue and provide information as requested by the Sponsor in addition to that requested on the SAE Report form. Information must include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality. Supporting documentation such as hospital discharge summaries or appropriate laboratory reports should also be sent to the Sponsor. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor. The Investigator will ensure that information reported immediately by telephone or other means and information entered on the SAE Report form is accurate and consistent.

#### **10.6.7.1 Reporting of Infusion Reactions**

The signs and symptoms of an infusion reaction usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion.

**Infusion reactions should be recorded so that the presenting sign/symptom is part of the reported AE term(s) (e.g., chills or infusion reaction, fever).** Acute infusion reactions should not be classified as anaphylaxis unless symptomatic bronchospasm and/or allergy-related edema/angioedema is/are the principal clinical manifestation(s). Refer to Appendix 5 for the clinical criteria for diagnosis of anaphylaxis.

The start of the infusion reaction with respect to the administration of the investigational product as well as the duration of each symptom should be recorded.

The intensity of the infusion reaction (refer to Section 10.6.5.4 for definitions of mild, moderate, or severe infusion reactions) and causal relationship (i.e., related or not related) to the investigational product (refer to Section 10.6.5.3 ) should be determined and reported.

#### **10.6.8 Other Significant Adverse Events**

Clinical laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and/or any events that lead to an intervention (including premature discontinuation or prolonged infusion time of the investigational product, or significant additional concomitant therapy) will be reported and evaluated as AEs.

Any clinically important changes noted during interim or final physical examinations, ECGs, x-rays, or any other potential safety assessments, whether or not these procedures are required by the protocol, must also be collected, and if serious recorded on the SAE Report form, when possible, in order for the Sponsor to collect additional information about that

abnormality, including information regarding relationship to KHK4083 or placebo, any action taken, and resolution.

### **10.6.9 Pregnancy Reporting**

This process is aimed at ensuring the appropriate monitoring of the potential risk related to investigational product exposure of pregnant women and/or fetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all subjects following exposure to the investigational product (KHK4083 or placebo).

**Female study subjects:** The subject must be advised by the Investigator to inform the Investigator immediately if she suspects she may be pregnant.

**Male study subjects:** The subject must be advised by the Investigator to inform the Investigator immediately if they suspect their partner became pregnant after the subject was administered investigational product.

When a study subject reports a pregnancy (post-KHK4083 administration) to the Investigator, KHK4083 should be stopped immediately and a pregnancy test should be arranged for the subject (or their partner) by the Investigator within 7 days of the pregnancy being reported.

In the case of pregnancy, the Investigator must immediately notify the Sponsor of this event and report the pregnancy on the Pregnancy Surveillance Form. This includes a study subject as well as the partner of a study subject who becomes pregnant while the subject was receiving investigational product. Every attempt will be made to follow the pregnancy to conclusion to obtain information regarding the outcome.

### **10.6.10 Safety Management during the Study**

The Sponsor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes AEs considered to be medically significant and making recommendations with the input of the Medical Monitor regarding further conduct of the study. The Safety Monitoring Committee will meet as needed in addition to the scheduled times according to the monitoring plan. Refer to Section 6.3 for details on the safety monitoring plan.

## **10.7 Appropriateness of Measurements**

All assessments and measurements are appropriate and generally regarded as standard care or medical practice.

# **11 DATA HANDLING AND QUALITY ASSURANCE**

## **11.1 Electronic Case Report Forms and Source Documentation**

Subject data will be entered into study eCRFs, transmitted electronically to the data management vendor and the Sponsor, and combined with data provided from other sources. Management of clinical data will be performed in accordance with applicable industry standards and data cleaning procedures to ensure the integrity of the data. It is the responsibility of the investigative site to prepare and maintain the adequate and accurate eCRFs that have been designed by the Sponsor to record all observations and other data pertinent to the clinical investigation. The eCRFs are used to record information collected in the performance of this study and that will be entered into the electronic data capture (EDC) system. These eCRFs are organized as an ordered series of electronic data entry modules specific for each scheduled and unscheduled study visit.

The investigative site EDC users will exercise due diligence in ensuring that study data are entered accurately and in their entirety from the investigative site's source documents and flow sheets into the appropriate data entry fields. Only staff listed on the "Delegation of Authority" page in the study file notebook and who have been appropriately trained to use the EDC system will be issued a user identification code allowing them to make entries and edits to the EDC system and to respond to queries. Only the Investigator will be issued a user identification code allowing the application of an electronic signature to a completed study subject record signifying the data has been reviewed and verified as complete and accurate.

By signing this protocol, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations. In addition for US investigative sites, compliance is required with all applicable provisions of the Health Insurance Portability and Accountability Act (HIPAA) and its implementing regulations.

## **11.2 Clinical Data Management**

Data management will be carried out by the contract research organization selected by the Sponsor. The Sponsor will provide oversight and will have the overall responsibility for the

processing and quality control of the data. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

Management of clinical data will be performed in accordance with applicable industry standards and data cleaning procedures to ensure the integrity of the data, e.g., removal of errors and inconsistencies in the data.

### **11.3 Archiving**

Electronic case report forms, including queries and audit trails, will be retained by the Sponsor, while the Investigator will receive a copy of the site data in the Portable Document Format on a compact disc-read only memory following study completion.

All study documentation at the investigative site and the Sponsor's site will be archived in accordance with ICH E6-GCP.

## **12 STATISTICAL METHODS AND PLANNED ANALYSIS**

### **12.1 General Statistical Considerations**

All categorical variables will be summarized by counts and percentages. Descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum) for continuous variables will be utilized. All summaries and analyses conducted will be by treatment cohort (KHK4083 dose levels; combined KHK4083; and placebo) and by visit. The specifics for these outputs will be described in detail within the Statistical Analysis Plan (SAP). The last pre-administration observation will be used as the Baseline value for calculating post-administration changes from Baseline. For efficacy assessments, Baseline is defined as Week 0. Data obtained and entered into the database will be provided in separate data listings showing individual subject values. The planning and reporting of statistical analysis will be carried out as described in the Sponsor's work instructions and standard operating procedures (SOPs) governing clinical studies.

### **12.2 Populations to be Analyzed**

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);
- **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.

Major protocol deviations will be assessed through the study team's review and the handling of these deviations described in the SAP.

### **12.2.1 Subject Disposition**

The number of subjects enrolled and completed/discontinued for each of the periods (Screening, Induction Therapy, Induction Therapy Follow-up Period, OLE/LTE Therapy, and LTE Therapy Follow-up Period) will be presented. A summary of reasons for discontinuation will be provided. The number of subjects in the Safety Analysis Set and FAS will be provided as well as the number of subjects who were excluded from each analysis set. The reasons why subjects were excluded from any analysis set will be summarized and listed individually.

### **12.2.2 Demographic and Baseline Disease Characteristics**

Summaries will include demographics (including age, race, ethnicity, and sex), height, body weight, and Baseline values for UC assessment in the Safety Analysis Set. All demographic data, including medical/surgical history and physical examination results of note, will be listed by subject.

### **12.2.3 Prior and Concomitant Medications**

The *World Health Organization Drug Dictionary* will be used to classify prior and concomitant medications by Therapeutic Class and Preferred Term. 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.

Prior and concomitant medications will be summarized separately in the Safety Analysis Set.

### **12.2.4 Investigational Product Exposure and Compliance**

Extent of exposure for each subject will be calculated as total amount of investigational product administered for the entire Treatment Period. Extent of exposure and total number of doses administered for each treatment during Induction Therapy and OLE/LTE Therapy will be summarized as well as the number of doses administered to subjects by period.

## 12.3 Efficacy Analysis

All efficacy analyses will be performed in the FAS unless otherwise specified.

### 12.3.1 Primary Efficacy Analysis

The primary efficacy variable is the change from Baseline (Week 0) in mucosal score presented by the mMES at Week 12 for 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. *(Note: For all other subjects who receive KHK4083 at dose levels different than the recommended dose in Parts A and B of Induction Therapy, this efficacy variable will be considered the main secondary variable.)* The primary variable will be used for an exploratory efficacy analysis using a linear model with Baseline values as a covariate to estimate the difference between treatment cohorts (each KHK4083 dose level versus placebo).

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.

### 12.3.2 Secondary Efficacy Analyses

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 as follows:

- The percentages of subjects with at least a 1-point improvement in their mMES from Baseline (Week 0) to Week 12.
- The percentages of subjects with at least a 1-point improvement in their modified Baron endoscopic score from Baseline (Week 0) to Week 12.
- The mean change in UCEIS (0 to 8) and subscores from Baseline (Week 0) to Week 12.
- The percentage of subjects with a mucosal healing (the mMES  $\leq$  1) at Week 12.
- The change from Baseline (Week 0) in total Mayo Clinic score (0 to 12) at Week 12.
- The change from Baseline (Week 0) in partial Mayo Clinic scores (0 to 9; without sigmoidoscopy) at Weeks 2, 4, 6, 8, 10, and 12.

- The percentages of clinical response (the change from Baseline in the total Mayo Clinic score  $\leq -3$  and the percentage change from Baseline in the total Mayo Clinic score  $\leq -30\%$  to Week 12, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of  $\leq 1$ ).
- The percentages of clinical remission (a total Mayo Clinic score  $\leq 2$  and no subscores  $> 1$ ) at Week 12.

Treatment (each KHK4083 dose level versus placebo) comparisons by cohort will be performed with the linear model for all secondary efficacy analyses of continuous variables.

### **12.3.3 Exploratory Efficacy Analysis**

Clinical improvement (changes from Baseline [Week 0] to Week 52 in the total Mayo Clinic score) at Week 52 will be summarized. In addition, change from Baseline (Week 0) in partial Mayo Clinic scores (without sigmoidoscopy) 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).

Clinical response at Week 52 will be summarized. Clinical remission will be summarized at Week 52.

At Weeks 12 and 52, durable clinical response and durable clinical remission (present at both Weeks 12 and 52), and glucocorticoid-free clinical remission at Week 52 will be summarized.

Remission (mMES of 0 or 1, stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0) rates at Weeks 12 and 52 will be summarized.

The percentage of subjects with mucosal healing at Week 52 will be summarized. 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; and/or mean change from Baseline in the UCEIS score) at Week 52.

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 LTE Therapy Follow-up Period visits (Weeks 56, 60, and 64).

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.

Treatment (each KHK4083 dose level versus placebo) comparisons by cohort and OLE/LTE will be performed with the linear model for all exploratory efficacy analyses of continuous variables.

Exploratory analyses are described in detail in the SAP.

#### **12.3.4 Sample Size Determination**

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 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.

#### **12.3.5 Significance Level**

All statistical analyses in this Phase 2 study will be descriptive or exploratory, and no adjustment to control Type I error will be performed.

### **12.4 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Analyses**

#### **12.4.1 Pharmacokinetic Analyses**

All subjects with sufficient quantifiable data will be included in the PK analysis. Serum concentration data will be summarized with descriptive statistics at each scheduled time point. Individual serum concentrations at each sampling time point for KHK4083 will be presented by listings. Descriptive summary statistics of serum concentrations including means, ranges, SD, and percent coefficient of variation (%CV) will be presented. Individual and mean concentrations versus time will be plotted on linear and semi-logarithmic scales.

Concentration-time data for Cohorts 1 - 3 (Induction Therapy - Part A and LTE Therapy) will be analyzed individually by non-compartmental analysis methods using actual elapsed times relative to the last dosing. The following PK parameters will be summarized:  $C_{max}$ ,  $t_{max}$ ,  $C_{min}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\tau}$ ,  $AUC_{0-\infty}$ ,  $t_{1/2}$ ,  $CLs$ ,  $V_{ss}$ ,  $V_z$ , and  $R_{ac}$ . The PK parameters for KHK4083 will be

summarized by dose level and Treatment Period (i.e., Induction Therapy and LTE Therapy). All PK parameters will be summarized using descriptive statistics (mean, SD, maximum, median, minimum, and %CV).

A sparse PK sampling strategy was planned for Cohort 4 (Induction Therapy - Part B and LTE Therapy), therefore population PK analysis using mixed-effect modeling will be applied to the data from both Cohorts 1 - 3 (Part A) and Cohort 4 (Part B). The PK exposure parameters will be calculated using a final population PK model.

The dose proportionality of KHK4083 PK exposure parameters will be assessed using the Power Model for Cohorts 1 - 3 (Induction Therapy - Part A and OLE/LTE Therapy). The PK exposure parameters include  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ , as appropriate. The PK-PD relationships will be explored using graphic tools or modeling as needed.

Additional details of the PK and PK-PD analyses will be addressed in a separate PK-PD Analysis Plan.

#### **12.4.2 Pharmacodynamic Analyses**

The PD parameters will be determined in subjects with moderately active UC and summarized by dose level and Treatment Period (i.e., Induction Therapy - Part A and Part B, and OLE/LTE Therapy). For the delayed-type hypersensitivity assay, values will be summarized at Screening and Week 10 for selected investigative sites. For fecal calprotectin, mean change and mean percentage change from Baseline (Week 0) at Week 12 and median values at Weeks 2, 12, and 52 will be analyzed for subjects who received the recommended dose. For the wr-CRP assays, mean change and mean percentage change from Baseline (Week 0) at Week 12 and median values at Weeks 2 through 12 and at Weeks 24, 36, 52, and 64 will be analyzed for the subjects who received the recommended dose. The details will be described in the PK-PD Analysis Plan.

#### **12.4.3 Immunogenicity Analyses**

The immunogenicity of KHK4083 will be determined in subjects with moderately active UC. The percentage of subjects with confirmed anti-KHK4083 antibodies will be summarized by dose level and Treatment Period (i.e., Induction Therapy - Part A and Part B, and OLE/LTE Therapy), visit (week), and overall. The effect of positive anti-KHK4083 antibodies on the PK, and possibly efficacy and safety, will be explored.

## **12.5 Analyses of Safety Data**

The overall safety and tolerability of KHK4083 compared to placebo administered in multiple IV doses will be determined for reported AEs (including SAEs), physical examinations, vital signs, body weight, 12-lead ECGs, and clinical laboratory tests. All summaries will be prepared for the Safety Analysis Set.

All subjects will be assessed from the signing of the ICF until 16 weeks after the last dose for potential AEs. Treatment-emergent adverse events (TEAEs) will be grouped and tabulated by MedDRA Preferred Terms (PT) and SOC. 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., Induction Therapy and OLE or LTE Therapy) and by cohort (KHK4083 versus placebo) during Induction Therapy or KHK4083 dose level versus placebo during OLE/LTE Therapy.

Secondary safety variables in each cohort (Induction Therapy) or KHK4083 dose level (LTE Therapy) will be:

- Serum chemistry, hematology, coagulation profile, and urinalysis parameters;
- Vital signs (systolic and diastolic blood pressure, radial pulse rate, and respiration rate);
- Incidence of abnormal 12-lead ECG findings.

Subject listings, summary tables, and figures including the change over time and shift tables will be generated for vital signs (including body temperature, systolic and diastolic blood pressure, radial pulse rate, and respiratory rate), 12-lead ECGs, body weight, and clinical laboratory assessments (serum chemistry, hematology, coagulation profile, and urinalysis). The results from physical examination will be presented in the subject data listings.

## **12.6 Procedures for Missing, Unused, and Spurious Data**

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

## **12.7 Rules for Excluding Subjects from Analysis**

All dosed subjects will be included in the analyses unless otherwise specified. The Sponsor will decide whether any subject or any individual values belonging to a subject will be excluded from the evaluations when the protocol violation is considered to have a negative impact on the scientific aspects and interpretation of the study results. If the subject has

received any investigational product (KHK4083 or placebo), all available safety data will be used. The reason(s) for any exclusion will be described in the final Clinical Study Report.

### **12.8 Procedures for Reporting Deviations from Original Statistical Plan**

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

## **13 SPECIAL REQUIREMENTS AND PROCEDURES**

### **13.1 Institutional Review**

Before starting this study, the protocol (authorized by the Sponsor) will be submitted to the regulatory/local health authorities (in accordance with local regulations) and to the IRB/IEC for evaluation. The protocol will also be signed by the Principal Investigator before submission to the IRB/IEC. The study will not start before the IRB/IEC gives written approval or a favorable opinion in accordance with ICH E6-GCP and all applicable regulatory/local health authorities give approval or a favorable opinion as required.

No changes from the final approved (authorized) protocol will be initiated without the IRB's/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistics or administration. The Sponsor will authorize and the Principal Investigator(s) will sign the protocol amendment prior to submission to the IRB/IEC. Protocol amendments should be submitted to the IRB/IEC without delay. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation, and will be addressed as such during the reporting of the study.

### **13.2 Ethical Considerations**

The Investigator is responsible for conducting the study in full accordance with the protocol, US Food and Drug Administration (FDA), Code of Federal Regulations (CFR), Title 21, Parts 50, 56, and 312, the October 2013 revision of the Declaration of Helsinki, the GCP Guideline, approved by the ICH, and any applicable national and local laws and regulations. Inability to comply with these standards by any participating investigative site will be documented.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/IEC and obtaining written approval for this study. Approval will be obtained prior to the initiation of the study.

### **13.3 Investigator's Responsibilities**

#### **13.3.1 Overall Responsibilities**

The Investigator(s) is/are responsible for conducting the study in full accordance with the protocol and the 2013 revision of the Declaration of Helsinki, the GCP: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigative site participating in this study that cannot comply with these standards will be documented.

#### **13.3.2 Subject Informed Consent**

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated ICF before any procedures or assessments are initiated and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangement/policy are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the Investigator will sign, date and time the ICF after the subject has signed, dated and recorded the time. The Investigator(s) will keep the original ICFs and copies will be given to the subjects.

#### **13.3.3 Confidentiality Regarding Study Subjects**

Particular attention is required to the regulations provided by the US FDA under the Freedom of Information Act providing, in part, that information furnished to Investigators and IRBs will be kept confidential by the FDA (i.e., only for information maintained in confidence by the Investigator and IRB).

The Investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material (including materials from all examinations including colonoscopies) submitted to the Sponsor, subjects will not be identified by their names, but by subject identification numbers.

Personal medical information may be scrutinized for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorized persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

## **13.4 Study Monitoring**

Study monitoring will be performed in accordance with ICH E6-GCP, the protocol, and applicable local regulations.

### **13.4.1 Direct Access to Source Data/Documents**

By signing this protocol, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of HIPAA and its implementing regulations.

The monitor(s), auditor(s), authorized personnel of the Sponsor, health authority inspector(s) or their agents, and authorized members of IECs/IRBs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with regulatory/local requirements.

## **13.5 Audit and Inspection**

According to ICH E6-GCP, the Sponsor or regulatory authorities may audit the investigative site. The Quality Assurance Unit of KKD, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The Investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

### **13.5.1 Record Retention**

Study data and other essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, these documents should be retained for a longer period if required by the applicable legal requirements. The Sponsor (or its designee) will inform the Investigator, in writing, as to when these documents no longer need to be maintained.

### **13.5.2 Investigator Information**

By signing this protocol, the Investigator recognizes that certain personal identifying information with respect to the Investigator, and all sub-Investigators and study investigative

site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials;
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, affiliates, and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the Investigator's name and business contact information may be included when reporting certain SAEs to regulatory agencies or to other Investigators. By signing this protocol, the Investigator expressly consents to these uses and disclosures.

In order to facilitate contact between Investigators, the Sponsor may share an Investigator's name and contact information with other participating Investigators upon request.

### **13.5.3 Compliance with Law, Audit, and Debarment**

By signing this protocol, the Investigator agrees to:

- 1) Conduct the study in an efficient and diligent manner and in compliance with this protocol, GCP, and all applicable regulatory requirements.
- 24) Complete, and/or update the FDA Form 1572 in a timely manner, and conduct the study in accordance with the specifications on Page 2 of FDA Form 1572.
- 25) Allow monitoring, audits, IRB/IEC review, and regulatory agency inspection of study-related documents and procedures; and provide for direct access to all study-related source data and documents.
  - a) Promptly and fully disclose to the Sponsor, and make available all source documentation at their investigative site upon the request for inspection by representatives of the Sponsor, IRB/IEC, or any regulatory agencies.
  - b) Promptly inform the Sponsor of any regulatory agency inspection conducted for this study.
  - c) Promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.
- 26) Provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.
- 27) Immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or,

to the best of the Investigator's knowledge, threatened. Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on the Sponsor's studies.

- 28) Provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by US FDA regulations (CFR, Title 21, Part 54), and other financial regulatory agencies. The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided. This requirement extends to sub-Investigators. This may involve the transmission of information to countries that do not have laws protecting personal data. Refer to Section 13.6 for additional details.

The ICH E6-GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the study, if the subject has a primary physician and if the subject agrees to the primary physician being informed.

In the event the Sponsor prematurely terminates a particular investigative site, KKD will promptly notify that investigative site's IRB/IEC.

#### **13.5.4 Administrative**

All references to the Sponsor/KKD in this section include all designees, e.g., Contract Research Organizations or Consultants acting on behalf of the Sponsor.

#### **13.6 Financial Disclosure**

Financial disclosures by the Investigator(s) (or investigating institution) and the Sponsor will comply with local regulations.

According to US FDA CFR, Title 21, Part 54, the Sponsor is required to completely and accurately disclose or certify information concerning the financial interests of an Investigator (or investigating institution) who is not a full-time or part-time employee to the FDA. Therefore, the Investigator(s) (or investigating institution) must provide the Sponsor with sufficient, accurate financial certification that none of the following financial arrangements (further defined in US FDA CFR, Title 21, Part 54.2) exist with the Sponsor or fully disclose the nature of the arrangement. This financial disclosure also applies to any financial arrangements that exist between the Sponsor and the Investigator's spouse(s) or dependent children.

### **13.7 Insurance**

This study is covered under the Sponsor's Liability Insurance Policy. A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

### **13.8 Publication Policy**

The study is part of a multicenter study; accordingly, the Institution and Principal Investigator of the study agree that the first publication of the results of the study shall be made in conjunction with the presentation of a joint, multicenter publication of the study results with the Investigators and the Institutions from all appropriate sites contributing data, analyses and comments. However, if such a multicenter publication is not submitted within twelve (12) months after the database has been locked, abandonment or termination of the study at all sites, or after Sponsor confirms there will be no multicenter study publication, the Institution and/or such Principal Investigator may publish the results from the institution site individually in accordance with the following requirements. Prior to submission of any materials for publication or presentation, the Institution will provide such materials or manuscript to the Sponsor for review. Details of the Sponsor's publication policy can be found in the Clinical Trial Agreement.

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## **15 APPENDICES/ATTACHMENTS**

## Appendix 1 Primary and Secondary Efficacy Definitions

<b>Term</b>	<b>Definition</b>
Clinical Improvement (Week 12)	A reduction, i.e., 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 9).
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 $\leq 2$ and no subscores $> 1$ .
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 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.
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.
Mucosal Healing (Week 12)	An mMES of 0 or 1.

**Appendix 2 Mayo Clinic Scoring System for Assessment of Ulcerative Colitis Activity (Score 0 to 12) with Modified Mayo Endoscopy Subscore**

**Score Range: 0 to 12<sup>a, b</sup>**

**Stool Frequency (subject to establish his/her ‘normal’ frequency)<sup>c</sup> (Subscore 0 to 3):**

- 0 = Normal number of stools for this subject
- 1 = 1 to 2 stools more than normal
- 2 = 3 to 4 stools more than normal
- 3 = 5 or more stools more than normal

**Rectal Bleeding (most severe bleeding of day to be recorded)<sup>c</sup> (Subscore 0 to 3):**

- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passes

**Endoscopy Findings<sup>b</sup> (Subscore 0 to 3):**

- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern)
- 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

**Physician’s Global Assessment<sup>c, d</sup> (Subscore 0 to 3):**

- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

a: Higher scores indicate more severe disease. The total Mayo Clinic score (0 to 12) is a sum of the four subscores.

b: Partial Mayo Clinic scores (0 to 9) exclude the Endoscopy Findings subscore because no endoscopy is performed.

Endoscopy Findings subscore is amended by removing mild friability from a subscore of 1; thus any friability, even if mild, results in an endoscopic subscore of at least 2.

c: Based on a review of the subject’s diary. Mayo Clinic subscores will be derived from the diaries over 2 to 3 qualifying days that are closest to each visit.

d: Based on subject’s daily recollection of abdominal discomfort and general sense of well-being, and other observations (e.g., physical findings and the subject’s performance status).

**Appendix 3                      Modified Baron Endoscopic Scoring System (5-point Scale)**

**5-point Scale:**

0 = normal mucosa, not friable

1 = granular mucosa with abnormal vascular pattern, not friable

2 = friable mucosa, no spontaneous bleeding

3 = micro-ulcerations with spontaneous bleeding

4 = gross ulceration

**Appendix 4**                      **Ulcerative Colitis Endoscopic Index of Severity**  
(Modified scoring based on scale provided in Travis, 2012)

<b>Descriptor (score most severe lesions)</b>	<b>Likert Scale Anchor Points</b>	<b>Definition</b>
<b>Vascular pattern</b>	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
<b>Bleeding</b>	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
<b>Erosions and ulcers</b>	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny ( $\leq 5$ mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger ( $> 5$ mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

**Appendix 5**

**Clinical Criteria for the Diagnosis of Anaphylaxis**

(US Food and Drug Administration, Guidance for Industry  
Immunogenicity Assessment for Therapeutic Protein Products -  
Appendix A)

## APPENDIX A

### 1) Diagnosis of Anaphylaxis

The diagnosis of anaphylaxis is based on the following three clinical criteria, with anaphylaxis considered as highly likely when one of these criteria is fulfilled (Sampson, 2006):

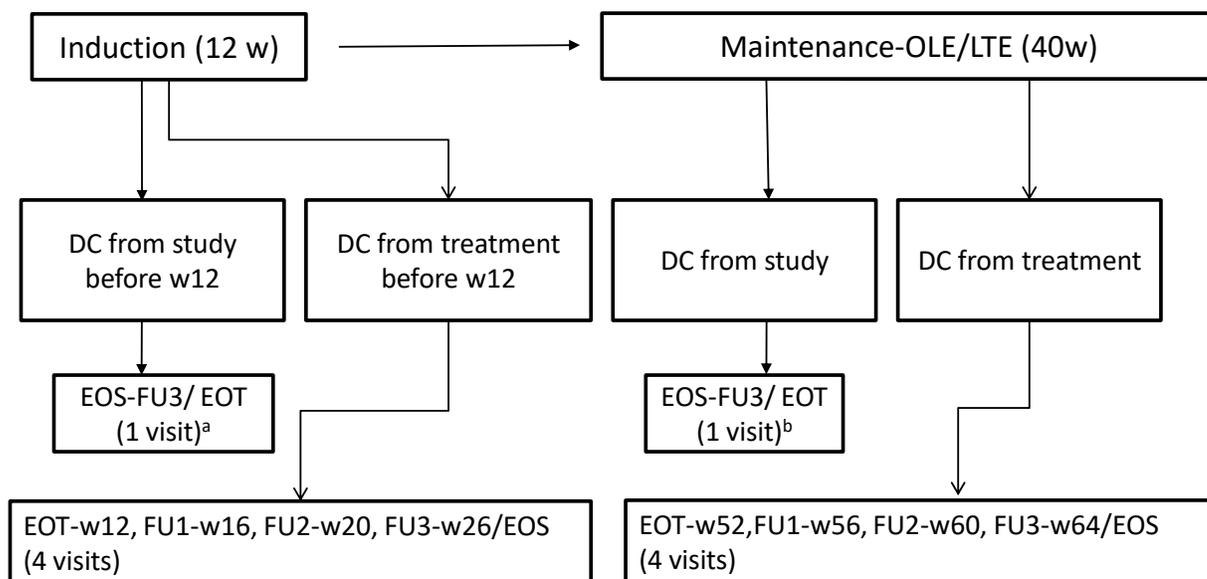
- a) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), **and at least one of the following**:
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- b) Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):
  - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- c) Reduced blood pressure after exposure to *known allergen for that patient* (minutes to several hours):
  - Infants and children: low systolic blood pressure (age specific) or greater than 30-percent decrease in systolic blood pressure
  - Adults: systolic blood pressure of less than 90 mm Hg or greater than 30-percent decrease from that person's baseline

Although none of the clinical criteria provide 100-percent sensitivity and specificity, it is believed that these criteria are likely to capture more than 95 percent of cases of anaphylaxis (Sampson, 2006).

Laboratory tests for evaluating anaphylaxis:

At present, there are no sensitive and specific laboratory tests to confirm the clinical diagnosis of anaphylaxis. Skin testing and in vitro diagnostic tests to determine the level of specific IgE antibodies directed against the therapeutic protein product, mediator release, or basophil activation may be useful for characterizing the underlying pathophysiology and may provide insight into potential mitigation strategies (Simons, 2010; Lee and Vadas, 2011). However, the results of unvalidated tests should be interpreted with caution; and the clinical relevance of positive results from unvalidated tests may be uncertain during product development.

### Appendix 6 Follow-up and End-of-Study for Subjects who Discontinued During the Study



DC=discontinuation; EOT=end-of-treatment; FU=follow-up; LTE=long-term extension; OLE=open-label-extension; w=week

a: EOT visit within 2 weeks after the last dose of IP. Endoscopy will be performed if the subject discontinues more than 8 weeks after Baseline visit.

b: EOT visit within 4 weeks after the last dose of IP. Endoscopy will be performed if the subject discontinues more than 8 weeks after Week 12 visit.