Protocol KAN-101-03

A PHASE 2A DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF KAN-101 IN PARTICIPANTS WITH CELIAC DISEASE

Statistical Analysis Plan
(SAP)

Version: 6

Date: 03Feb2025

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study KAN-101-03 is based on the protocol Amendment 1 dated 20Mar2024.

Table 1 Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 06Nov2023	Original 06Sep2023	Not Applicable (N/A)	N/A
2 05Apr2024	Amendment 1 20Mar2024	The protocol was amended based on PART 1 questions received from the EU CTA, submitted 27 Nov 2023 To address FDA comments, received in November 2023	Section 6, Interim Analyses (IA) updated to provide rationale for having the IA. Section 3, mITT population was added for supplementary analysis purpose. Section 5 and Appendix I, added supplementary analysis for the primary and secondary efficacy endpoints using all collected data (ie, treatment policy) for FAS. Section 5 and Appendix I, added supplementary analysis for the secondary/exploratory efficacy endpoints using all collected data for mITT. Appendix 2, added analysis visit window for ADA.

Table 1 Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
3 07Jun2024	Amendment 1 20Mar2024	Update Section 6 interim analyses	Added sample size calculation and alpha spending for interim analysis in the design section. Changed "intercurrent events" to be included in the population definition. Eliminated the mITT population and replaced with SAS (ITT) population as a sensitivity analysis. Included a BAS (Biopsy Analysis Set).
4 16Oct2024	Amendment 1 20Mar2024	Update Appendix 2.1 Added summary and analysis for Nausea Score and Vomiting Frequency and change from baseline	Analysis windows were updated. Sections 2.3 and 5.3.2, CDSD 1-Day, 3-Day, 7-Day Nausea Score and Vomiting Frequency and change from baseline at each timepoint post-gluten challenge will be summarized and analyzed using Wilcoxon Signed-rank test for within treatment paired comparison and Wilcoxon Rank Sum test for comparison between placebo vs each of KAN group.
5 13Dec2024	Amendment 1 20Mar2024	Made clarification for CDSD average calculation. Made clarification for analysis set.	Section 2.3, 5.3.2, Appendix 2.2, CDSD average score calculation was updated. Intent-To-Treta (ITT) was removed from Sections 3, 5.1.2, 5.2.2.

Table 1 Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
		Marsh-Oberhuber score is categorical	Section 5.3.1, Baseline and Day 29 Marsh-Oberhuber score will be summarized with frequency and percentage. Change from baseline to Day 29 will be summarized using shift table
		COVID-19 pandemic is over.	Section 5.5, COVID-19 listing and summary were removed
		Map IL-2 and CDSD data to Day 15 if first GC is on Day 14 or Day 16.	Appendix 2.1, Analysis window for IL-2 and CDSD was added (Table 8)
03Feb2025	Amendment 1 20Mar2024	How to handle CDSD multiple records on a same day	Section 5.3.2, added a statement: If there are multiple records on a same day, the earliest one will be used for analysis.
		Make GC start day window wider	Section 5.3.2, added weekly time definition of analysis window for Week 2 and Week 3 when the first GC day is at Day 17. Appendix Table 8, analysis window for first GC day was changed from "Day 14 to Day 16" to "Day 14 to Day 17".

Table 1 Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
		Updated analysis windows for PGIS, PGIC, vital signs, and lab tests.	Appendix 2 Tables 3, 4, 5: analysis windows of Day 15 and Day 29 were updated to relative to the first (or second) GC day instead of absolute study day.

1. INTRODUCTION

Study KAN-101-03 is a multi-center, double-blind, placebo-controlled Phase 2a study to examine whether KAN-101 confers protection from gluten challenge (GC)-induced histological changes in the duodenum and to further evaluate the safety/tolerability of KAN-101 in adult patients (≥18 years) with celiac disease (CeD).

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study KAN-101-03. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

1.1. Study Objectives, Endpoints, and Estimands

Study objectives, corresponding endpoints, and estimands are provided in the Table 2 below.

Table 2 Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Assess the ability of KAN-101 to attenuate GC-induced changes in duodenal histology as measured by changes in villus-height:crypt depth (Vh:Cd) ratio after a 2-week GC.	Changes from baseline in Vh:Cd ratio as assessed by esophagogastroduodenoscopy (EGD) with biopsy after 2-week GC (at Day 29).	Estimand 1: a hypothetical estimand (Section 1.1.1).
Secondary:	**Secondary:**	**Secondary:**
Examine the impact of KAN-101 on biomarker response (interleukin-2 [IL-2]) in peripheral blood following GC	IL-2 change from Day 15 (first day of GC) pre GC to Day 15 post GC.	Estimand 2: a hypothetical estimand (Section 1.1.2).
Determine the effects of KAN-101 on histologic features (intraepithelial lymphocytes [IELs] density) in duodenum biopsies following 2-week GC.	Changes from baseline in IEL density in duodenum biopsy after 2-week GC (at Day 29)	Estimand 3: a hypothetical estimand (Section 1.1.2).
Assess the safety and tolerability of KAN-101 in participants with CeD.	Incidence and severity of treatment emergent adverse events (TEAEs) as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (or higher).	Not applicable.
	Incidence and titer of KAN-101 anti-drug antibodies (ADA).	Not applicable.
Assess the pharmacokinetics (PK) of multiple doses of KAN-101 in participants with CeD.	Plasma concentration of KAN-101, and associated KAN-101 parameters: AUC_{inf}, AUC_{last}, C_{max}, T_{max} and $t_{½}$	Not applicable.

Table 2 Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
Evaluate changes in histological features (Marsh-Oberhuber score) after 2-week GC	Changes from baseline in Marsh-Oberhuber score after 2-week GC (at Day 29)	Not applicable.
Assess the impact of KAN-101 administration on the incidence of CeD symptoms before and during GC as measured using CDSD v2.1.	Changes from baseline in symptoms PROs including: CDSD v2.1, PGIC and PGIS over time.	Not applicable.
Assess whether KAN-101 affects the incidence and/or titer of post-GC celiac serology.	Change from baseline in incidence and titer of tTG IgA and DGP IgG at Day 42.	Not applicable.

1.1.1. Primary Estimand

Estimand 1: The primary estimand is the hypothetical estimand, which estimates the treatment effect of KAN-101 vs placebo (PBO) for change from baseline in Vh:Cd ratio. It includes the following 5 attributes:

- Population: Participants who receive all 3 doses of study intervention and complete at least 7 days of GC and do not receive prohibited medications.
- Variable: Vh:Cd ratio change from baseline at Day 29.
- Treatment conditions: KAN-101 or PBO.
- Intercurrent Events: Events are addressed in the analysis set definition.
- Population level summary: The least-squares mean (LSM) difference of the change from baseline in Vh:Cd ratio between KAN-101 and PBO.

1.1.2. Secondary Estimand

Estimand 2 is the hypothetical estimand, which estimates the treatment effect of KAN-101 vs PBO for IL-2. It includes the following 5 attributes:

- Population: Participants who receive all 3 doses of study intervention, complete GC at Day 15 and do not receive prohibited medications.
- Variable: log transformed IL-2 change from pre GC to post GC at Day 15.
- Treatment condition: KAN-101 or PBO.
- Intercurrent Events: Events are addressed in the analysis set definition.

- Population level summary: The LSM difference of the change from pre GC to post GC at Day 15 (log transformed) between KAN-101 and PBO.

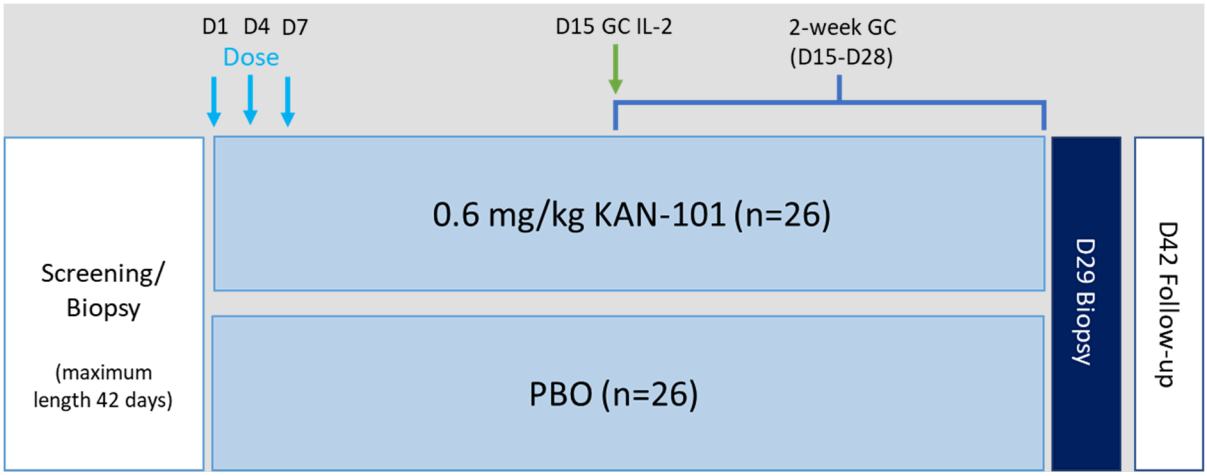
Estimand 3 is the hypothetical estimand, which estimates the treatment effect of KAN-101 vs PBO for change from baseline in duodenal IEL density. It includes the following 5 attributes:

- Population: Participants who receive all 3 doses of study intervention and complete at least 7 days of the 2-week GC and do not receive prohibited medications .
- Variable: IEL change from baseline at Day 29.
- Treatment conditions: KAN-101 or PBO.
- Intercurrent Events: Events are addressed in the analysis set definition.
- Population level summary: The LSM difference of the change from baseline in IEL between KAN101 and PBO.

1.2. Study Design

Study KAN-101-03 is a multi-center, double-blind, PBO-controlled Phase 2a study to examine whether KAN-101 confers protection from GC-induced histological changes in the duodenum and to further evaluate the safety/tolerability of KAN-101 in adult patients (≥18 years) with CeD. Approximately fifty-two patients (26 patients per arm) will be randomized 1:1 to 0.6 mg/kg KAN-101 (Arm 1) or PBO (Arm 2).

Figure 1 Study Design Schema



1.3. Sample Size

A sufficient number of participants will be screened to achieve approximately 52 treated participants (26 per study arm). The sample size calculation is based on the primary efficacy estimand and its endpoint, changes from baseline in the ratio of Vh:Cd at Day 29 visit. With

an overall 2-sided type I error rate of 5%, the study will have approximately 94% power under a sample size of 26 participants per arm to detect a treatment difference in LSM of 0.50 in change in ratio of Vh:Cd between treatment arms, assuming that the common standard deviation is 0.5 and the difference between the means is 0.5. To adjust for multiple looks, the O'Brien-Fleming adjustment is applied to control overall type I error rate to ensure that the overall Type I error rate remains at 5%. The interim analysis will be evaluated at significance level 0.003 and the final look will be evaluated at significance level 0.049.

2. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

2.1. Primary Endpoint

- Change from baseline in Vh:Cd ratio as assessed by EGD with biopsy after 2-week GC (at Day 29).

  The biopsy will be performed at screening and Day 29, or ET visit. The Baseline is the last non-missing Vh:Cd ratio at screening.

2.2. Secondary Endpoints

- GC IL-2 change from Day 15 (first day of GC) pre-GC to Day 15 post GC.

  GC IL-2 will be log transformed prior to calculating the change.

- Change from baseline in IEL density in duodenum biopsy after 2-week GC (at Day 29).

  The biopsy will be performed at screening and Day 29, or ET visit. The Baseline is the last non-missing IEL density at screening.

- Incidence and severity of TEAEs as assessed by the CTCAE.

See Section 2.5.1.

- Incidence and titer of KAN-101 ADA.

  Positive of ADA will be assessed at Days 1, 7, 29, 42 or early termination (ET) visit.

- Plasma concentration of KAN-101, and associated KAN-101 parameters: AUC_{inf}, AUC_{last}, C_{max}, T_{max} and $t_{½}$.

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/K_{el})$, where Clast is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time to first occurrence of C_{max}	Observed directly from data.
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/K_{el}$, where K_{el} is the terminal Phase rate constant calculated by a linear regression of the loglinear - concentration time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression

- a. If data permits.

2.3. Exploratory Endpoints

- Changes from baseline in Marsh-Oberhuber score assessed via EGD with biopsy after 2-week GC.
- The biopsy will be performed at screening and Day 29, or ET visit. Baseline is the last non-missing Marsh-Oberhuber score at screening.
- CDSD

- CDSD is a patient reported outcome (PRO) questionnaire collected daily. The version 2.1 includes 5 severity items and 3 frequency supplement questions (see Appendix 2.2) that will be collected daily.

    - CDSD Total Score is the sum of all 5 severity items. The CDSD Weekly Average Total Score will be calculated , for details on the calculation see below, Section 5.3.2 and Appendix 2.2.

    - The CDSD Gastrointestinal (GI) Domain Score is the sum of items 1-4. The CDSD Weekly Average Gastrointestinal (GI) Domain Score will be calculated, for details on the calculation see below, Section 5.3.2 and Appendix 2.2 .

    - For CDSD Nausea score and vomiting frequency, in addition to weekly average score, 3-day average will be derived as well (every 3 days start from Day 15 GC until Day 41). If 2 observations are missing, the 3-day average score will not be calculated. Day 15 Nausea score and vomiting frequency will be analyzed as well.

- For CDSD Total score, GI Domain score, individual severity item and frequency supplement question, the Baseline value is the average of most recent 7-day interval scores before Day 1 (not include Day 1) with at least 4 days with non-missing scores, and will be used as the baseline to calculate the change from baseline to the 1-day, 3-day average and weekly average. If there are ≥4 days missing scores in any 7-day interval before Day 1, the baseline value is set as missing.

- For post-baseline weekly average score calculation, Week 1 is from Day 1 to Day 7, Week 2 is from Day 8 to the day before Day 15 GC, Week 3 is from the day after Day 15 GC to Day 21. The number of days for Week 2 and Week 3 maybe equal to, less than, or greater than 7. See Section 5.3.2 for the details. The weekly average score is the weekly sum score divided by the number of days with non-missing in that week. If daily scores are missing for more than half of total days in a specific week, the average score is missing for that week.

- Change from baseline at each timepoint = observed (or derived as described above) value at each timepoint – baseline.

- The observed value and the change in PGIS

- PGIS is a PRO questionnaire designed to assess the patient's impression of disease severity over the past week (see Appendix 2.3) that is collected at baseline (Day 1), Day 15, 29, 42, or ET visit.

- Change from baseline at each timepoint = observed value at each timepoint – baseline. Baseline is the last non-missing value up to Day 1.

- The observed value in PGIC

- PGIC is a PRO questionnaire designed to assess the patient's impression of the overall change in participant's celiac disease since receiving study intervention (see Appendix 2.4) that will be collected at Days 15, 29, 42, or ET visit.
- Change from baseline in incidence and titer of tTG IgA and DGP IgG at Day 42.
- Other exploratory biomarkers may be analyzed at a later date.

2.4. Demographic and Baseline Variables

Demographic and baseline characteristics include:

- Age
- Sex
- Race
- Ethnicity
- Height (in cm)
- Weight (in kg)
- Body Mass Index
- Duration of CeD
- Duration of gluten-free diet (GFD)
- CeD Serology at diagnosis
- Histology at diagnosis

2.5. Safety Endpoints

Safety will be assessed by medical history, vital signs, clinical laboratory tests, and the reporting of AEs, in all participants who received any portion of study intervention. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Clinicians will review individual participant data throughout the conduct of the study to ensure participants' wellbeing.

2.5.1. Adverse Events

Incidence and severity of TEAEs is the Secondary endpoint.

An adverse event (AE) is considered TEAE to a given treatment if the event start date is on or after the treatment period start date and before end of study.

The CTCAE displays Grades 1 through Grade 5 with unique clinical descriptions of severity for each AE based on below general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

2.5.2. Safety Laboratory Data

Safety laboratory testing will be performed at Screening, Days 1, 4, 7, 15, 29, 42, or ET visit. The details are listed in below table.

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs, %) Eosinophils (Abs,%) Monocytes (Abs,%) Basophils (Abs,%) Lymphocytes (Abs,%) PT aPTT INR	Urea and creatinine Serum cystatin C eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total and direct bilirubin Alkaline phosphatase Uric acid Albumin Total protein Magnesium Amylase Lipase Phosphorus	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	At screening: FSH[b] Pregnancy test (β-hCG)[c] HBsAg and HBcAb. HBsAb and HBV DNA as reflex tests Hepatitis C antibody and HCV RNA as reflex test HIV HLA genotype and CeD serology (eg, HLA DQ2.5 and HLA-DQ8 testing[d], tTG and DGP IgA/IgG) Biomarker: IL-2 PK/ADA

a. Only if Urinary Tract Infection is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. For confirmation of postmenopausal status only.
c. A serum pregnancy test is required at screening. Following screening, local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β–hCG for female participants of childbearing potential.
d. For re-screening, the HLA does not need to be repeated and CeD serology (the tTG and DGP antibody tests) should only be repeated if >3 months have elapsed from end assessment.

2.5.3. Vital Signs

Vital signs will be assessed at Screening, Days 1, 4, 7, 15, 29, 42, or ET visit.

3. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled	All participants who sign the ICD.
Biomarker Analysis Set (BAS)	All participants who are randomly assigned to study intervention, receive any portion of study intervention, and have completed the GC on Day 15, without prohibited medications. Participants will be analyzed according to the intervention they are randomized.
Full analysis set (FAS)	All participants who are randomly assigned to study intervention, receive all 3 doses of study intervention, and complete at least 7 days of the 2-week GC without prohibited medications. Participants will be analyzed according to the intervention they are randomized.

Analysis Set	Description
Per protocol set (PPS)	The PPS will include all participants from the FAS who complete all 14 days of the 2-week GC and biopsies, and without major protocol violations that might affect the evaluation of the effect of study intervention on the primary endpoint. The PPS will be used in sensitivity analyses of the primary and secondary endpoints. Specific reasons for warranting exclusion from this population will be documented prior to database lock.
Safety analysis set (SAS)	All participants who receive any portion of study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set (PKAS)	All participants who receive any portion of study intervention and have at least one concentration value.

4. GENERAL METHODOLOGY AND CONVENTIONS

4.1. Hypotheses and Decision Rules

This protocol is designed to establish the superiority of KAN-101 to PBO for the primary endpoint of the change in Vh:Cd ratio at Day 29. The null hypothesis is that there is no difference between KAN-101 and PBO, and the alternative hypothesis is that there is a significant difference between KAN-101 and PBO. KAN-101 will be considered superior to PBO with the change in Vh:Cd ratio at Day 29, at the interim look, if the difference is statistically significant at the 2-sided 0.003 level. Even if significance is reached at the interim analysis, no decision to stop the trial will be made unless a safety concern arises. Statistical significance will be evaluated at the end of study at the 2-sided 0.049 level.

4.2. General Methods

In general, count and percent will be presented for categorical variables. Number of observations, mean, standard deviation (SD), minimum (min), 1st, 2nd, 3rd quartiles, and maximum (max) will be presented for continuous variables. The coefficient of variation (CV, defined as SD/Mean; %CV=100*CV), geometric mean (GM), and geometric mean ratio (GMR) will also be included, where appropriate. Graphics will be used to present the data.

4.2.1. Analyses for Continuous Endpoints

For continuous endpoints, the change from baseline will be analyzed by timepoint using analysis of covariance (ANCOVA) model with treatment as a factor, baseline as a covariate. For endpoints without baseline, analysis of variance (ANOVA) model with treatment as a factor will be used for the analysis. Comparison of KAN-101 to PBO (providing LSM of the treatments, LSM of the treatment difference, p-value and 95% CI) will be generated.

4.3. Methods to Manage Missing Data

If a PK concentration value is below Lower Limit of Quantification (LLOQ), that concentration value will be treated as 0 for all analysis. For IL-2, values below LLOQ will be treated as ½LLOQ. Other missing values will not be imputed for safety, efficacy and PK endpoints.

5. ANALYSES AND SUMMARIES

In general, observed values and change from baseline (where applicable) will be descriptively summarized by treatment group with number of observations, mean, SD, min, 1st, 2nd (median) and 3rd quartiles, and max, unless otherwise specified. For log-transformed values the geometric mean and 95% CI will be presented with the summary statistics.

Data will be summarized and analyzed by treatment group for the main population of interest and a separate sensitivity/supplementary analysis(ses) based on the chosen analysis set from Section 3).

Endpoint	Analysis Set Applied for Main Analysis	Analysis Set Applied for Sensitivity/Supplementary Analysis
Biopsy (Vh:Cd, IEL Density Marsh-Oberhuber Score)	Full Analysis Set	Per Protocol Set and Safety Analysis Set
Biomarker (IL2)	Biomarker Analysis Set	Per Protocol Set and Safety Analysis Set
PK	PK Analysis Set	N/A
PRO (CDSD, PGIS, PGIC)	Full Analysis Set	N/A
Demography and Safety	Safety Analysis Set	N/A
ADA	Safety Analysis Set	N/A

5.1. Primary Endpoint Analysis: Vh:Cd

The primary endpoint is the change from baseline in Vh:Cd ratio as assessed by EGD with biopsy after 2-week GC (at Day 29).

Raw data will be descriptively summarized by treatment group with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, and max for the FAS.

5.1.1. Main Analysis

The Hypothetical estimand, Estimand 1 (Section 1.1.1) will be addressed with the following analysis: change from baseline in Vh:Cd ratio at Day 29 will be analyzed using ANCOVA model (Section 4.2.1) for the FAS Population. The LSM change from baseline and associated 95% CI, LSM difference of the change from baseline between KAN-101 and PBO, 95% CI, and p-value will be presented along with summary statistics.

5.1.2. Sensitivity/Supplementary Analysis

Per-protocol (PP) additional sensitivity/supplementary analyses will be performed for change from baseline in Vh:Cd ratio at Day 29 visit using the same approach of main analysis as described above,5.1.1 with the analysis sets stated in Section 5. Same analysis will be performed for SAS as well.

5.2. Secondary Endpoints

5.2.1. GC IL-2

GC IL-2 change from pre GC to post GC at Day 15 will be analyzed.

5.2.1.1. Main Analysis

Log transformed GC IL-2 change from pre GC to post GC at Day 15 will be analyzed using ANCOVA model as described in Section 4.2.1 based on Estimand 2 (see Section 1.1.2) for the BS. The LSM change (log transformed), LSM difference of LSM change (log transformed) between KAN-101 and PBO, 95% CI, and p-value will be presented. Exponentially transformed values for LSM, LSM difference, 95% CI will be presented as well.

5.2.1.2. Sensitivity/Supplementary Analysis

The above analysis will also be performed for the log transformed GC IL-2 for the analysis sets stated in Section 5 as a supplementary analysis.

5.2.2. IEL density in duodenum biopsy

Summary statistics will be provided for observed values for IEL and the change from baseline at Day 29.

5.2.2.1. Main Analysis

IEL change from baseline at Day 29 will be analyzed using ANCOVA model as described in Section 4.2.1 based on Estimand 3 (see Section 1.1.2) for the FAS. The LSM change, LSM difference of LSM change between KAN-101 and PBO, 95% CI, and p-value will be presented.

5.2.2.2. Sensitivity/Supplementary Analysis

The above analysis will be performed for PPS and the SAS as a sensitivity/supplementary analyses.

5.2.3. Incidence and Severity of TEAEs as Assessed by the CTCAE

See safety Section 5.5.1.

5.2.4. Incidence of Development of ADA During the Study

Participants positive for ADA (screening, confirmatory, specificity and titer) will be summarized by treatment group and timepoint with number and percent for the SAS.

5.2.5. PK Concentration

PK concentration will be descriptively summarized by treatment group and nominal timepoints with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, max for PKAS. Line plot will be provided by treatment group for mean (+/-SD) concentration-time profiles using linear and semi-log scale

5.2.6. PK Parameters

PK parameters listed in Section 2.2 (AUC_{inf}, AUC_{last}, C_{max}, T_{max}, and $t_{1/2}$) will be descriptively summarized by treatment group with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, max, GM, and %CV for PKAS. No GM and %CV for T_{max}.

5.3. Tertiary/Exploratory

5.3.1. Change from baseline in Marsh-Oberhuber score at Day 29

Marsh-Oberhuber score at baseline and Day 29 observed values will be summarized with number of observations, frequency and percentage for each category. The shift from baseline to Day 29 will be summarized as well. The analysis sets used for this endpoint is found in Section 5.

5.3.2. CDSD

The weekly average score of each severity item and frequency question of CDSD (Diarrhea, Abdominal Pain, Bloating, Nausea, Number of times Vomiting, Tiredness, Number of Bowel Movements and Number of events of Diarrhea) as well as the weekly average CDSD Total Score, weekly average CDSD GI Domain Score (see Section 2.3 and Appendix 2.2) and change from baseline will be descriptively summarized as stated in Secton 5 for each treatment group by timepoint.

The change from baseline for weekly average of each of the 5 severity items and 3 frequency questions, the weekly average CDSD Total Score, and the weekly average CDSD GI Domain Score will be analyzed using ANCOVA models in Section 4.2.1 by timepoint. LSM of the treatments with 95% CI, LSM of the treatment difference with PBO, p-value and 95% CI will be generated.

If there are multiple records on a same day, the earliest one will be used for analysis.

The analysis set(s) used for these endpoints are found in Section 5.

Weekly Time Definitions:

	Regardless the day of Day 15 GC	Day 15 GC is at day 14	Day 15 GC is at day 15	Day 15 GC is at day 16	Day 15 GC is at day 17
Baseline	Day -7 to -1				
Week 1	Day 1 to 7				
Week 2		Day 8 to 13	Day 8 to 14	Day 8 to 15	Day 8 to 16
Week 3		Day 14 to 21	Day 15 to 21	Day 16 to 21	Day 17 to 21
Week 4	Day 22 to 28				
Week 5	Day 29 to 35				
Week 6	Day 36 to 42				

In addition, the change from baseline in CDSD Nausea score and vomiting frequency for Day 15, 3-day average and 7-day average (weekly average) score, will be summarized as stated above, and analyzed within placebo and KAN treatment, evaluating the paired difference from baseline using the Wilcoxon Signed-rank test. The Mann-Whitney U test (Wilcoxon Rank Sum test) will be used to test the difference in the change from baseline for placebo vs KAN-101. The median difference between treatment groups estimated by the Hodges–Lehmann method along with the 95% CI will be reported as well.

Line plots by treatment group will be provided for LSM 95% CI).

5.3.2.1. PGIS

PGIS and change from baseline will be descriptively summarized as stated in Section 5. The change from baseline will be analyzed using ANCOVA models in Section 4.2.1 by timepoint. LSM of the treatments, LSM of the treatment difference with PBO, p-value and 95% CI will be generated.

The analysis will be performed for all collected data as stated in Section 5.

5.3.2.2. PGIC

PGIC will be descriptively summarized as stated in Section 5.

The analysis will be performed for all collected data as stated in Section 5.

5.3.2.3. Subset Analyses

N/A

5.4. Baseline and Other Summaries and Analyses

5.4.1. Baseline Summaries

Demographic and baseline characteristics listed in Section 2.4 will be summarized according to Sponsor's reporting standards for the SAS.

5.4.2. Study Conduct and Subject Disposition

Participants evaluation, disposition, discontinuation will be summarized for the SAS according to Sponsor's reporting standards.

5.4.3. Study Treatment Exposure

The exposure to study drug will be summarized by treatment group for number of doses of study intervention applied for the SAS.

5.4.4. Gluten Challenge

GC will be summarized by number and percentage of participants completed number of days of GC for the SAS, FAS, and PPS. GC can be mixed with liquid such as water, lactose-free mild or lactose-free chocolate milk, fruit juice (no prune, pear, or apricot), sports drink. The number and percentage of participants with mixture to GC will be summarized by treatment, mixture type, and GC day for the SAS, FAS, and PPS

5.4.5. Concomitant Medications and Non-Drug Treatments

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Sponsor's reporting standards.

5.5. Safety Summaries and Analyses

Safety analyses will be based on the SAS.

All clinical TEAEs, SAEs, withdrawal due to AEs, vital signs and safety laboratory data will be reviewed on an ongoing basis during the study to evaluate the safety of participants.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Sponsor's Standards. Categorical outcomes (eg, AEs) will be summarized by participant counts and percentage. Continuous outcome will be summarized using N, mean, median, SD, min, max. Participant listings will be produced for these safety endpoints accordingly.

5.5.1. Adverse Events

Adverse events will be summarized for the SAS according to Sponsor's reporting standards for

- TEAEs
- Serious AEs (SAEs)
- TEAEs will be summarized by the number of participants reporting any TEAE, system organ class (SOC), preferred term (PT), severity, relationship to investigational product (based on investigator's judgement).
- CTCAE is used to grade the severity of AEs. TEAEs related to GC and infusion-related reactions (IRR) will also be summarized separately.
- SAEs will be summarized by SOC and PT, and individual SAEs will be listed by participant.

A list of subjects who prematurely discontinue from the study due to an AE will be provided as well.

5.5.2. Safety Laboratory Data

Clinical safety laboratory values listed in Section 2.5.2 and change from baseline and clinically significant change will be summarized according to Sponsor's standards.

5.5.3. Vital Signs

Vital signs and change from baseline and clinically significant change will be summarized according to Sponsor's standards.

6. INTERIM ANALYSES

An interim analysis (IA) will be conducted to assess efficacy and safety after approximately 13 participants from each group have completed through the Day 29 visit including histology assessments.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per the sponsor's or sponsor designee's SOPs will be documented in the Interim Analysis Plan.

7. CHANGES FROM PROTOCOL

- Sample size calculation was updated to include consideration for multiple looks. Decision rules were also updated.
- Sensitivity/Supplementary analyses were updated with the new populations.

- Prohibited medications are considered in the study set definitions with the other intercurrent events (noncompliance with study medications and noncompliance with gluten challenge).

- An additional study set was added for IL2 called the BAS.

8. REFERENCES

1. Protocol KAN-101-03 Amendment 1 20March2024.

APPENDICES

Appendix 1. Summary of Efficacy/Exploratory Analyses

Endpoint	Analysis Type	Population	Analysis Model
Change from baseline in Vh:Cd ratio at Day 29	Summary	FAS	N/A
	Main analysis	FAS	ANCOVA with terms treatment, baseline
	Sensitivity/supplementary analysis	PPS, SAS	ANCOVA with terms treatment, baseline
GC IL-2 (log-transformed) change from Day 15 pre-GC to Day 15 post GC	Summary	BAS	N/A
	Analysis	BAS	ANCOVA with terms treatment, baseline
	Sensitivity/supplementary analysis	PPS, SAS	ANCOVA with terms treatment, baseline
Changes from baseline in IEL density in duodenum biopsy after 2-week GC (at Day 29)	Summary	FAS	N/A
	Analysis	FAS	ANCOVA with terms treatment, baseline
	Sensitivity/supplementary analysis	PPS, SAS	ANCOVA with terms treatment, baseline

Endpoint	Analysis Type	Population	Analysis Model
CDSD change from baseline at each timepoint	Summary	FAS	N/A
	Analysis	FAS	ANCOVA with terms treatment, baseline
	Sensitivity/supplementary analysis	PPS, SAS	ANCOVA with terms treatment, baseline
CDSD 1-Day, 3-Day, 7-Day Nausea Score and Vomiting Frequency and change from baseline at each timepoint post-gluten challenge	Summary	FAS	Observed cases
	Analysis	FAS	All data collected will be included regardless of intercurrent events. Missing data will not be imputed. Wilcoxon Signed-rank test for change from baseline within each group
	Analysis	FAS	All data collected will be included regardless of intercurrent events. Missing data will not be imputed. Mann-Whitney U test (Wilcoxon

Endpoint	Analysis Type	Population	Analysis Model
			Rank Sum test) for comparison of placebo vs KAN group for change from baseline
PGIS change from baseline at each timepoint	Summary	FAS	N/A
	Analysis	FAS	ANCOVA with terms treatment, baseline
PGIC at each timepoint	Summary	FAS	N/A
	Analysis	FAS	ANOVA with term treatment
Marsh- Oberhuber score	Summary	FAS, PPS, SAS	N/A

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Analysis Windows in Reporting

Analysis windows will be used for PROs and vital signs, and laboratory tests.

If more than one observation from the same participant falls into the same analysis window, the value closest to the targeted day will be used as the observation for that visit. All observations will, however, be included in the listings.

Table 3 Analysis Windows for PGIS and PGIC

Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening up to first dosing date)	Day 1	Last observation up to and including first dosing date
Day 15	Day 15	After last dose – First day of GC
Day 29	Day 29	Second day of GC – Day 35
Day 42	Day 42	Day 36 – end of study

Table 4 Analysis Windows for Vital Signs

Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening up to first dosing date)	Day 1	Last observation up to first dosing
Day 1 during dosing	Day 1 during dosing	Start of Day 1 dosing to end of Day 1 dosing
Day 1 after dosing	Day 1 after dosing	End of Day 1 dosing to end of Day 1
Day 4 before dosing	Day 4 pre-dosing	Day 2 - Day 4 pre-dosing
Day 4 during dosing	Day 4 during dosing	Day 4 start of dosing - Day 4 end of dosing
Day 4 after dosing	Day 4 after dosing	Day 4 end of dosing - end of Day 4
Day 7 before dosing	Day 7 pre-dosing	Day 5 - Day 7 pre-dosing
Day 7 during dosing	Day 7 pre-dosing	Day 7 start of dosing - Day 7 end of dosing
Day 7 after dosing	Day 7 after dosing	Day 7 end of dosing - end of Day 7
Day 15	Day 15 pre-GC	Day 8 - pre-GC of first GC day
Day 29	Day 29	After GC of first GC day – Day 35
Day 42	Day 42	Day 36 – end of study

Table 5 Analysis Windows for Laboratory Tests

Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening up to first dosing date)	Day 1	Last observation up to first dosing
Day 4	Day 4 pre-dosing	Day 1 after dosing - Day 4 pre-dosing
Day 7	Day 7 pre-dosing	Day 4 after dosing - Day 7 pre-dosing
Day 15	Day 15 pre-GC	Day 7 after dosing - pre-GC of first GC day
Day 29	Day 29	post-GC of first GC day – Day 35
Day 42	Day 42	Day 36 – end of study

Table 6 Analysis Windows for ADA

Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening up to first dosing)	Day 1 pre-dosing	Last observation prior to first dosing date
Day 7	Day 7 pre-dosing	Day 2 - Day 7 pre-dosing
Day 29	Day 29	Day 8 – Day 35
Day 42	Day 42	Day 36 – end of study

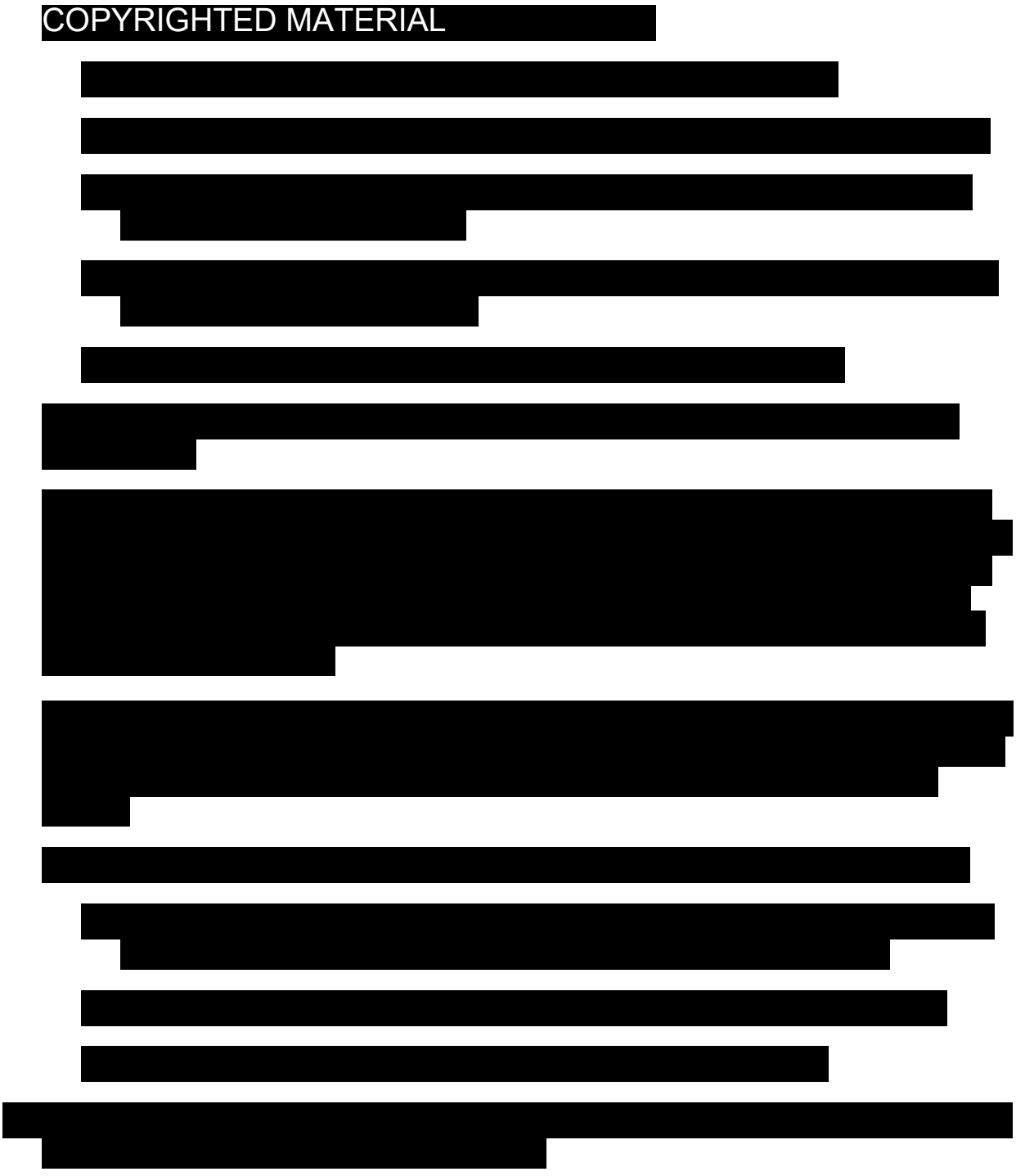
Table 7 Analysis Windows for biopsy endpoints (Vh:Cd ratio, IEL density, Marsh-Oberhuber score)

Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening up to first dosing)	Day 1 pre-dosing	Last observation prior to first dosing date
Day 29	Day 29	Day 22 – Day 43

Table 8 Analysis Windows for IL-2 and CDSD at Day 15 (first GC Day)

Visit Label	Targeted Day	Analysis window for data sets
Day 15	Day 15	The first GC day, Day 14 – Day 17

Appendix 2.2. Celiac Disease Symptom Diary (CDSD)



Appendix 2.3. Patient Global Impression of Severity (PGIS)

COPYRIGHTED MATERIAL

Appendix 2.4. Patient Global Impression of Change (PGIC)

COPYRIGHTED MATERIAL

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	Analysis of variance
AST	aspartate aminotransferase
AUC_{inf}	area under the plasma-concentration curve from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
BAS	Biomarker analysis set
BP	blood pressure
CDSD	celiac disease symptom diary
CeD	celiac disease
CI	Confidence interval
C_{max}	maximum observed concentration
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DSMB	data safety monitoring board
ET	early termination
FAS	full analysis set
GC	gluten challenge
GFD	gluten-free diet
GI	Gastrointestinal
GM	geometric mean
GMR	geometric mean ratio
ICD	informed consent document
IL-2	interleukin-2
IRR	infusion-related reactions
LLOQ	Lower Limit of Quantification
max	maximum
min	minimum
N/A	not applicable
PBO	placebo
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

Abbreviation	Term
PK	pharmacokinetic(s)
PKAS	PK analysis set
PRO	patient-reported outcome
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety analysis set
SD	standard deviation
SOC	system organ class
$t_{½}$	terminal phase half-life
TEAE	treatment -emergent adverse event
T_{max}	time to reach C_{max}
ULN	upper limit of normal