Protocol KAN-101-02

A PHASE 1B OPEN-LABEL/ PHASE 2 DOUBLE-BLIND PLACEBO-CONTROLLED STUDY FOR PHARMACODYNAMIC ACTIVITY, PHARMACOKINETICS, SAFETY AND TOLERABILITY OF KAN-101 IN PATIENTS WITH CELIAC DISEASE

Part A

Statistical Analysis Plan
(SAP)

Version: 3

Date: 13Jun2025

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study KAN-101-02 Part A is based on the protocol amendment dated 21Jun2023.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28OCT2022	Original 31Aug2022	Not Applicable (N/A)	N/A
2 10Jul2023	Amendment 1 21Jun2023	Protocol Amended	In Section 2.3, 6 mg/kg KAN 101 (cohort 3) was removed.
3 13Jun2025	Amendment 3 30Jan2024	Protocol Amended Study termination	Section 2, Part C was added. Section 6.3, the tertiary/exploratory endpoints will not be measured/reported.

2. INTRODUCTION

Study KAN-101-02 is a 3-part, multicenter Phase 1b/2 study of KAN-101 in participants with celiac disease (CeD) on a gluten-free diet (GFD). The 3 parts include: Part A – Open-label, multiple ascending dose (MAD); Part B – Double-blind, placebo (PBO)-controlled, parallel design; Part C – Double-blind, placebo (PBO)-controlled, parallel design.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study KAN-101-02 Part A. 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.

2.1. Modifications to the Analysis Plan Described in the Protocol

"Entered" analysis set is added to Section 4, it is not in the protocol.

2.2. Study Objectives, Endpoints, and Estimands

Study Part A objectives and corresponding endpoints are provided in the Table 2 below. Part A is open label. The primary objective is to evaluate the safety of KAN-101. There is no hypothesis testing. Estimands are not applicable for Part A.

Table 2. Objectives and Endpoints

Objectives	Endpoints
Primary:	
• 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).
Secondary:	
• Assess the pharmacokinetics (PK) of multiple doses of KAN-101 in participants with CeD.	• KAN-101 plasma exposure as data permit: AUC_{inf}, AUC_{last}, C_{max}, T_{max} and $t_{½}$.
Tertiary/Exploratory:	
• To further characterize the PK profile of KAN-101 following multiple doses in participants with CeD. • To evaluate the immunogenicity of KAN-101. • Examine the biomarker response (interleukin-2 [IL-2]) in peripheral blood following gluten challenge (GC) and after dosing.	• KAN-101 PK parameters, as data permit: AUC_{inf} (dn), AUC_{last} (dn), C_{max}(dn), CL, V. • Incidence of development of anti-drug antibodies (ADA) during the study. • Change in magnitude of IL-2 response pre-and-post GC in peripheral blood at Day 15.

2.3. Study Design

Study KAN-101-02 is a 3-part, multicenter Phase 1b/2 study of KAN-101 in participants with CeD on GFD. The 3 parts include:

- **Part A** – Open-label, multiple ascending dose
- **Part B** – Double-blind, PBO-controlled, parallel design
- **Part C** – Double-blind, PBO-controlled, parallel design

Part A is a Phase 1b, open-label, MAD 3+3 study design to assess the safety, tolerability and PK of KAN-101 in adult participants (18 to 70 years inclusive) with histology-confirmed CeD. Up to 6 participants who meet study inclusion/exclusion criteria may be randomized in the study.

Eligible participants will be administered IV study intervention on Day 1, Day 4, and Day 7. The dose cohorts planned for Part A are:

- 1.2 mg/kg (Cohort 1)
- 3.0 mg/kg (Cohort 2)

Participants who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn participant. No

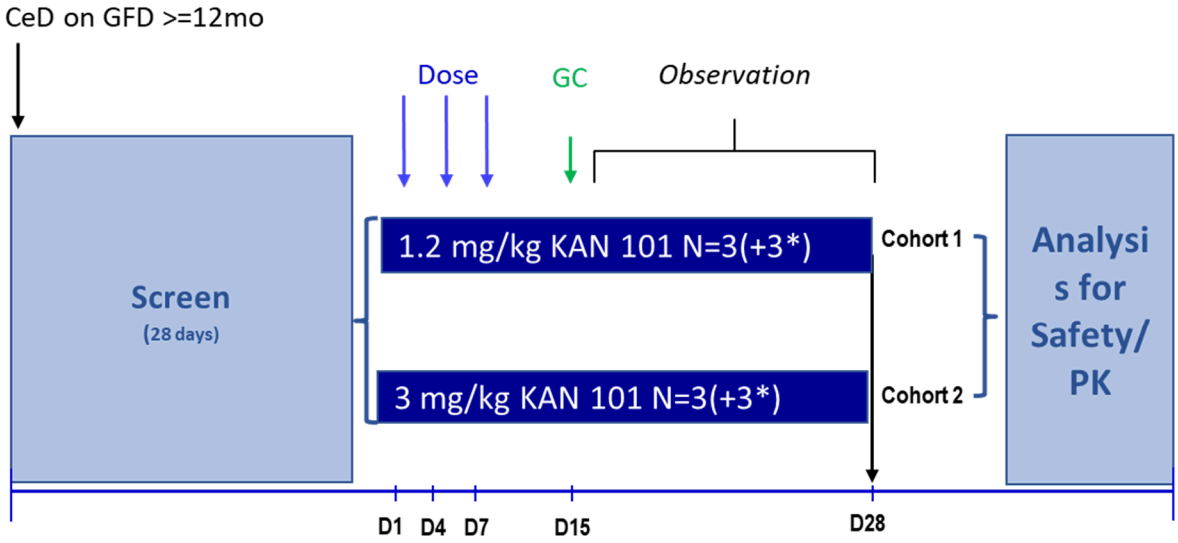
participant with a dose limiting toxicity (DLT) will be replaced. Each dose group (cohort) may have 3-6 participants.

Based on emerging data from previous and ongoing cohorts, doses planned may be repeated, modified and other doses may be explored in additional cohorts. If the exposures in the subsequent dose are projected to exceed the exposure limits pre-specified, that dose will not be explored.

All participants administered KAN-101 will return to the clinic on Day 15 to receive a 1-day 9g oral GC to assess exploratory endpoints (plasma IL-2 biomarker response to gluten and collect symptom information).

For Part A, a data safety monitoring board (DSMB) will review cumulative safety data through the dose escalation safety review period by cohort before opening a higher dose cohort. Initiation of the next dose cohort will commence once all participants in a cohort reach Day 15 prior to the GC, and upon acceptable safety review by DSMB and approval from sponsor.

Figure 1. Part A Study Design Schema



* Depending on safety and tolerability, each group may enroll 3 additional participants to establish the MTD.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- Incidence and severity of TEAEs as assessed by CTCAE.

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 (V5.0) 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.

3.2. Secondary Endpoints

- KAN-101 plasma exposure as data permit: 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 (Clast)	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	AUC_{last} + (Clast/K_{el}), where Clast is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time to first occurrence of C_{max}	
$t_{½}$[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.

3.3. Exploratory Endpoints

- KAN-101 PK parameters, as data permit: AUC_{last}(dn), AUC_{inf}(dn), C_{max}(dn), CL, V.

Parameter	Definition	Method of Determination
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}(dn)	Dose normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}(dn)	Dose normalized C_{max}	C_{max}/Dose
CL[a]	Apparent systemic clearance	Dose/AUC_{last}
V[a]	Apparent volume of distribution following IV dosing	Dose/AUC_{inf}×K_{el}

a. If data permits.

- Incidence of development of ADA during the study.
- Change in magnitude of IL-2 response pre-and-post GC in peripheral blood at Day 15.

IL-2 response to GC is IL-2 post-GC at Day 15 – IL-2 pre-GC at Day 15.

3.4. 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 GFD
- HLA genotype
- CeD Serology at diagnosis
- Histology at diagnosis

3.5. Safety Endpoints

Safety will be assessed by medical history, vital signs, clinical laboratory tests, and the spontaneous 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' well-being.

3.5.1. Adverse Events

Incidence and severity of TEAEs is the primary endpoint of Part A. See Section 3.1.

3.5.2. Safety Laboratory Data

Safety laboratory testing will be performed at Screening, Days 1, 4, 7, 15, 28, or early termination (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[a] INR[a]	Urea and creatinine 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[b]	At screening: • FSH[c] • Pregnancy test (β-hCG)[d] • Hepatitis B surface antigen and HbcAb. HBsAb and HBV DNA as reflex tests • Hepatitis C antibody and HCV RNA as reflex testHIV • HLA DQ2.5 and HLA DQ8 testing[e] • tTG and DGP IgA/IgG[f]

a. aPTT and INR tests are performed in Part A only.
b. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
c. For confirmation of postmenopausal status only.
d. 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.
e. 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.
f. For tTG, a result of <2 x ULN will be considered negative or weak positive. For DGP, a result of <30 U/mL will be considered negative or weak positive.

3.5.3. Vital Signs

Vital signs will be assessed at Screening, Days 1, 4, 7, 15, 28, or ET visit.

4. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined for Part A:

Analysis Set	Description
Entered	All participants who sign the informed consent document (ICD).
Enrolled	All entered participants who are assigned to study intervention in Part A.
Full analysis set (FAS)	All participants who receive any portion of study intervention in Part A.
Safety analysis set (SAS)	All participants who receive any portion of study intervention in Part A. It is the same as FAS.
PK analysis set (PKAS)	All participants who receive any portion of study intervention and have at least one concentration value in Part A.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Part A is open label. There is no hypotheses and decision rules.

5.2. General Methods

In general, count and percent will be presented for categorical variables. Number of observations, mean, standard deviation (SD), minimum (min), median, and maximum (max) will be presented for continuous variables. The coefficient of variation (CV), geometric mean (GM), geometric mean ratio (GMR) will also be included, where appropriate. Graphics may be used to present the data. All summaries will be performed by dose group.

5.3. Methods to Manage Missing Data

Missing values will not be imputed for safety, efficacy and PK endpoints. 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.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

The primary endpoint for Part A is incidence and severity of TEAEs. Adverse events will be summarized for SAS according to Sponsor's reporting standards for

- TEAEs
- Serious AEs (SAEs)

TEAEs will be summarized overall and Day 1 to Day 15 prior GC by dose group by the number of participants reporting any TEAE, system organ class (SOC), preferred term (PT), severity, relationship to investigational product. 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.

6.2. Secondary Endpoints

6.2.1. PK concentration

PK concentration will be descriptively summarized by dose group and nominal timepoints with number of observations, mean, SD, min, median, max for PKAS. Line plot will be provided by dose group for mean and individual concentration-time profiles using linear and semi-log scale, .

6.2.2. PK parameters

PK parameters listed in Section 3.2 (AUC_{inf}, AUC_{last}, C_{max}, T_{max}, and $t_{1/2}$) will be descriptively summarized by dose group with number of observations, mean, SD, min, median, and max, GM, and %CV for PKAS. No GM and %CV for T_{max}.

6.3. Exploratory Endpoints

The tertiary/exploratory endpoints will not be measured/reported due to study termination.

6.4. Subset Analyses

N/A

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics listed in Section 3.4 will be summarized according to Sponsor's reporting standards for SAS.

6.5.2. Study Conduct and Subject Disposition

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

6.5.3. Study Treatment Exposure

The exposure to study drug will be summarized by dose group for number of doses of study intervention received and number and percentage of participants who are compliant with the dosing regimen for the SAS. A participant is considered compliant with the dosing regimen if he/she receives 80% to 120% of the expected amount of study intervention, in accordance with the protocol.

6.5.4. Gluten Challenge

GC will be summarized by number and percentage of participants completed GC for SAS.

6.5.5. 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.

6.6. 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.

Separate listings and/or summaries may be produced for participants who are impacted by COVID-19, have protocol deviations, discontinue from study or study treatment due to the COVID-19 pandemic.

6.6.1. Adverse Events

See Section 6.1.

6.6.2. Laboratory Data

Clinical laboratory values and change from baseline and clinical significant change will be summarized according to Sponsor's standards.

6.6.3. Vital Signs

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

7. INTERIM ANALYSES

No formal interim analysis will be conducted for Part A. However, as Part A is an open label, dose escalation study, the cumulative safety data may be summarized at end of each cohort by dosing group for DSMB review and decision making for next step.

8. REFERENCES

1. Protocol KAN-101-02.

APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. Definition and Use of Analysis Windows in Reporting

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

If more than one observation from the same participant falls into the same visit 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 (Day -28) to up to first dosing date)	Day 1	Last observation up to and including first dosing date
Day 15	Day 15	Day 8 – Day 21
Day 28	Day 28	Day 22 – end of study

Table 4. Analysis Windowns for Vital Signs and Laboratory Tests

Visit Label	Targeted Day	Analysis window for data sets
Baseline (Screening (Day -28) to up to first dosing date)	Day 1	Last observation up to and including first dosing date
Day 4	Day 4 pre-dosing	Day 2 - Day 4 pre-dosing
Day 7	Day 7 pre-dosing	Day 5 - Day 7 pre-dosing
Day 15	Day 15 pre-GC	Day 8 - Day 15 pre-GC
Day 28	Day 28	Day 16 – end of study

Appendix 1.2. Celiac Disease Symptom Diary (CDSD)

[redacted]

Appendix 1.3. Patient Global Impression of Severity (PGIS)

[redacted]

Appendix 1.4. Patient Global Impression of Change (PGIC)

[redacted]

Appendix 2. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf} (dn)	dose normalized AUC_{inf}
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})
AUC_{last} (dn)	dose normalized AUC_{last}
BP	blood pressure
CDSD	celiac disease symptom diary
CeD	celiac disease
CL	apparent systemic clearance
C_{max}	maximum observed concentration
C_{max} (dn)	dose normalized C_{max}
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
min	minimum
max	maximum
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
V	apparent volume of distribution

Protocol KAN-101-02

A PHASE 1B OPEN-LABEL/ PHASE 2 DOUBLE-BLIND PLACEBO-CONTROLLED STUDY FOR PHARMACODYNAMIC ACTIVITY, SAFETY AND TOLERABILITY OF KAN-101 IN PATIENTS WITH CELIAC DISEASE

Part B

Statistical Analysis Plan
(SAP)

Version: 4

Date: 13Jun2025

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study KAN-101-02 Part B is based on the protocol amendment dated 30Jan2024.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28OCT2022	Original 31Aug2022	Not Applicable (N/A)	N/A
2 10Jul2023	Amendment 1 21Jun2023	Protocol amended	In Section 2.3, study drug arms are defined as 0.6 mg/kg, 1.2 mg/kg, and 3.0 mg/kg as active study drug arms and placebo in Part B
28Feb2024	Amendment 3 30Jan2024	Protocol amended	Section 2 and Section 2.3, Part C was added, Figure 1 ws updated. Section 2.2 Table 2 and Section 2.2.1, estimand 1 was changed to treatment policy, estimand 2 was removed. Section 3.1 and Section 3.3, some editorial changes. Section 5.1 was updated to reflect that there is no hypothesis testing for Part B. Section 5.1 was removed. No analysis for continuous endpoints. Section 6.1 was updated to reflect that only descriptive summary will be performed for the primary endpoint.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
			Main analysis and sensitivity analysis were removed for the primary endpoint. Sections 6.3.3, 6.3.4, 6.3.5 (old Sections 6.4.3, 6.4.4, 6.4.5 in version 2), analysis was removed. Section 6.6 (old Section 6.7), listings and/or summaries for participants impacted by COVID-19 were removed. Section 7, Interim analysis was removed. Appendix 1, Analysis related iterms were removed. Appendix 2.1, analysis windows were added for Immunogenicity data (Table 6).
13Jun2025	Amendment 3 30Jan2024	Study termination	Section 6.3 and Appendix 1, the exploratory endpoints (except section 6.3.2 Incidence of development of ADA during the study) will not be measured/reported.

2. INTRODUCTION

Study KAN-101-02 is a 3-part, multicenter Phase 1b/2 study of KAN-101 in participants with celiac disease (CeD) on gluten-free diet (GFD). The 3 parts include: Part A – Open-label, multiple ascending dose (MAD); Part B – Double-blind, placebo (PBO)-controlled, parallel design (participants have baseline gluten change at Day -21); Part C – Double-blind, PBO-controlled, parallel design (there is no baseline gluten change).

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study KAN-101-02 Part B. As the populations for Part B and Part C are different (Part B participants have to demonstrate a symptomatic response following a 1-day oral GC performed during Run-in. There is no such requirement for Part C). Part B and Part C data will not be combined for analysis. 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.

2.1. Modifications to the Analysis Plan Described in the Protocol

"Entered" analysis set is added to Section 4, it is not in the protocol. The definition of "Enrolled" analysis set is different from that in the protocol.

2.2. Study Objectives, Endpoints, and Estimands

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

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:		
• Examine the biomarker response (interleukin-2 [IL-2]) in peripheral blood following gluten challenge (GC) and after dosing.	• Change in magnitude of IL-2 response pre- and post-GC in peripheral blood from baseline (run-in) to Day 15.	• Estimand 1: a treatment policy estimand.
Secondary:		
• Assess the pharmacokinetics (PK) of multiple doses of KAN-101 in participants with CeD.	• KAN-101 plasma exposure as data permit: AUCinf, AUClast, Cmax, Tmax and t½.	• N/A.
• 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).	
Tertiary/Exploratory:		
• To further characterize the PK profile of KAN-101 following multiple doses in participants with CeD.	• KAN-101 PK parameters, as data permit: AUCinf (dn), AUClast (dn), Cmax(dn), CL, V.	• N/A.
• To evaluate the immunogenicity of KAN-101.	• Incidence of development of anti-drug antibodies (ADA) during the study.	
	• Incidence of CeD symptoms following GC as assessed by Patient Reported Outcomes	

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
• Assess the incidence of CeD symptoms before and after GC. • Assess durability of biomarker response in peripheral blood following GC. **Biopsy Substudy:** • To evaluate the impact of KAN-101 on histology from esophagoduodenoscopy (EGD) biopsy in participants with CeD. • Evaluate the potential relationship between histopathological state and response to 1 day GC	(PROs) including: celiac disease symptom diary (CDSD) v2.1, patient global impression of change (PGIC) and patient global impression of severity (PGIS). • Change in magnitude of IL-2 response pre-and-post GC in peripheral blood from baseline (run-in) to GC at Weeks 12, 24, and 36. • Change in magnitude of IL-2 response pre- and post-GC in peripheral blood from Day 15 to Weeks 12, 24, and 36. **Biopsy Substudy:** • Change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52. • Correlation between histological state, symptomatic response and biomarker responses (IL-2). (This analysis will be performed separately, not be included in the CSR)	

2.2.1. Estimand

Estimand 1: This estimand is a treatment policy, the observed data will be used for summary without regard to intercurrent events. It includes the following 5 attributes:

- Population: Participant with CeD as defined by the Part B inclusion and exclusion criteria.
- Variable: Change in magnitude of IL-2 response pre- and post-GC from baseline to Day 15.
- Treatment conditions: 3 dose groups of KAN-101 or PBO.
- Intercurrent Events: Intercurrent events will not be considered for analysis.
- Population level summary: Mean, geometric mean ratio of post-GC vs pre-GC in IL-2 at Day -21 and Day 15 by treatment.

2.3. Study Design

Study KAN-101-02 is a 3-part, multicenter Phase 1b/2 study of KAN-101 in participants with CeD on GFD. The 3 parts include:

- **Part A** – Open-label, multiple ascending dose
- **Part B** – Double-blind, PBO-controlled, parallel design (participants have baseline GC at Day -21)
- **Part C** – Double-blind, PBO-controlled, parallel design (without baseline GC)

Part B is a Phase 2, double-blind, PBO-controlled, parallel design study to characterize the biomarker response (plasma IL-2; primary endpoint) in peripheral blood following GC. Safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years inclusive) with histology-confirmed CeD will also be assessed.

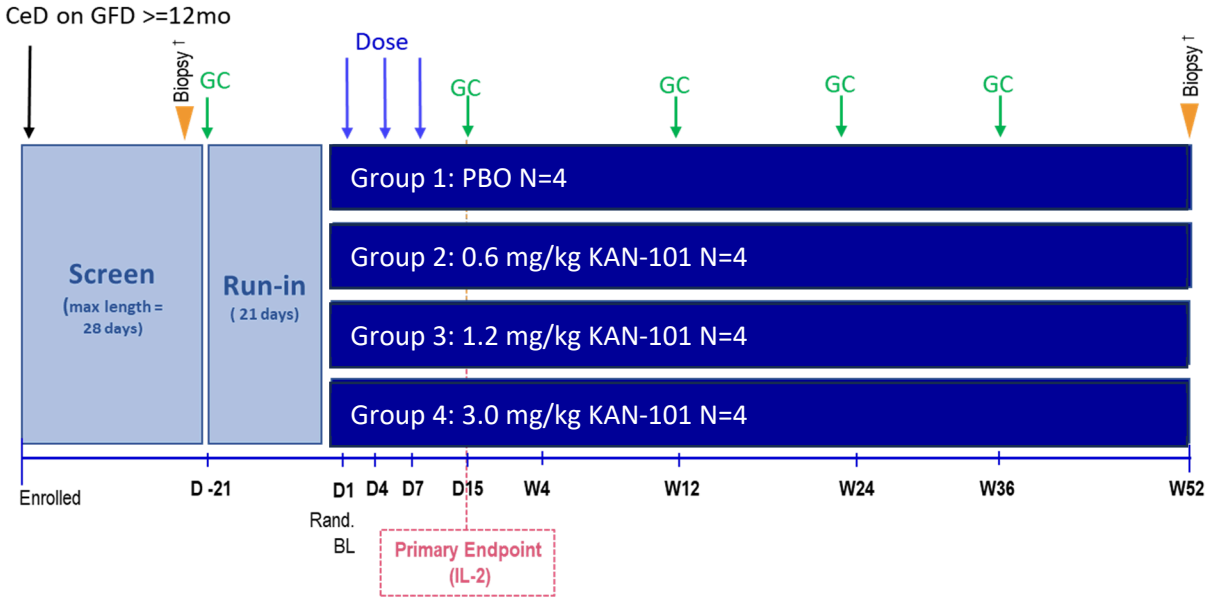
Eligible participants will undergo 1-day 9g GC on first day of run-in period (21 days before administration of first dose of study drug) to confirm symptomatic response to oral GC. 16 responders of GC will be randomized 1:1:1:1 and stratified by participation in biopsy substudy to one of the following 4 treatment groups and administered study intervention IV for 3 administrations (1 administration every 3 days starting at Day 1):

- PBO (Group 1)
- 0.6 mg/kg (Group 2)
- 1.2 mg/kg (Group 3)
- 3.0 mg/kg (Group 4)

All participants will return to the clinic at Day 15, Weeks 12, 24, and 36 to receive a 1-day 9 g oral GC to assess plasma IL-2 biomarker response to gluten and collect symptom information and follow-up visits on Day 28 and Week 52.

Participants participating biopsy substudy at applicable sites will receive biopsies at screening and Week 52.

Figure 1. Part B Study Design Schema



† Biopsy only collected as part of Biopsy Substudy at applicable sites.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- Change in magnitude of IL-2 response pre-and post-GC in peripheral blood from baseline (run-in) to Day 15.

The IL-2 response to GC is the difference of IL-2 between pre-GC and post-GC at each GC timepoint. The IL-2 response to GC and change in magnitude of IL-2 response will be presented by geometric mean ratio in summary.

3.2. Secondary Endpoints

- KAN-101 plasma exposure as data permit: 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 (Clast)	Linear/Log trapezoidal method

Parameter	Definition	Method of Determination
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	AUC_{last} + (Clast/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}	
$t_{½}$[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.

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

See Section 3.5.1.

3.3. Exploratory Endpoints

- KAN-101 PK parameters, as data permit: AUC_{last}(dn), AUC_{inf}(dn), C_{max}(dn), CL, V.

Parameter	Definition	Method of Determination
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}(dn)	Dose normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}(dn)	Dose normalized C_{max}	C_{max}/Dose
CL[a]	Apparent systemic clearance	Dose/AUC_{last}
V[a]	Apparent volume of distribution following IV dosing	Dose/AUC_{inf}×K_{el}

a. If data permits.

- Incidence of development of ADA during the study

  Positive of ADA will be assessed at Days 1, 7, 28, Weeks 12, 24, 36, 52 or early termination (ET) visit.

- The observed value and the change in CDSD

  CDSD is a patient reported outcome (PRO) questionnaire. The version 2.1 includes 5 severity items and 3 frequency supplement questions (see Appendix 2.2) that will be collected daily. Each individual item and question as well as the CDSD Total Score (calculation found in Appendix 2.2), CDSD GI Score will be summarized and analyzed. Baseline CDSD is the average of most recent 7-day scores prior to run-in GC (Day -21) (not include GC day) with at least 4 days with non-missing scores.. Weekly average and daily assessment at dosing days and GC days will be used for summary and analysis. If data are missing for more than 3 days for a participant within a week, the weekly average is set as missing for that participant at that week. Change from baseline at each timepoint = observed 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, 28, Weeks 12, 24, 36, 52, 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, 28, Weeks 12, 24, 36, 52, or ET visit.

- The observed value, response, and the change in magnitude of IL-2 response pre-and-post GC in peripheral blood from baseline (run-in) to GC at Weeks 12, 24, and 36. The IL-2 response to GC is the difference of IL-2 between pre-GC and post-GC at each GC timepoint. The change in magnitude of IL-2 is the change for IL-2 response to GC from baseline to each time point of Weeks 12, 24, and 36. The IL-2 response to GC and change in magnitude of IL-2 response will be presented by geometric mean ratio in summary.

- The observed value and the change in magnitude of IL-2 response pre- and post-GC in peripheral blood from Day 15 to Weeks 12, 24, and 36. The change in magnitude of IL-2 is the change for IL-2 response to GC from Day 15 to each time point of Weeks 12, 24, and 36. The IL-2 response to GC and change in magnitude of IL-2 response will be presented by geometric mean ratio in summary

- The observed value and the change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52 for substudy.

3.4. 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)
- HLA genotype
- CeD Serology at diagnosis
- Histology at diagnosis
- PGIS
- CDSD total score

3.5. Safety Endpoints

Safety will be assessed by medical history, vital signs, clinical laboratory tests, and the spontaneous 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' well-being. All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations. All safety analyses will be performed on the safety population. (See Section 6.6).

3.5.1. Adverse Events

Incidence and severity of TEAEs is the Secondary endpoint of Part B.

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 (V5.0) 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.

3.5.2. Safety Laboratory Data

Safety laboratory testing will be performed at Screening, Days 1, 15, Weeks 12, 24, 36, 52, 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	Urea and creatinine 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] • Hepatitis B surface antigen and HbcAb. HBsAb and HBV DNA as reflex tests • Hepatitis C antibody and HCV RNA as reflex testHIV • HLA genotype and CeD serology (eg, HLA DQ2.5 and HLA DQ8 testing[d], tTG and DGP IgA/IgG[e])

a. Only if UTI 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.
e. For tTG, a result of <2 x ULN will be considered negative or weak positive. For DGP, a result of <30 U/mL will be considered negative or weak positive.

3.5.3. Vital Signs

Vital signs will be assessed at Screening, run-in (Day -21), Days 1, 4, 7, 15, 28, Weeks 12, 24, 36, 52, or ET visit.

4. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined for Part B:

Analysis Set	Description
Entered	All participants who sign the ICD.
Enrolled (Randomized or assigned to study intervention)	All entered participants who are randomized to study intervention in Part B.
Full analysis set (FAS)	All participants who are randomly assigned to study intervation and receive any portion of study intervention in Part B. Participants will be analyzed according to the intervention they are randomized.
Safety analysis set (SAS)	All participants who receive any portion of study intervention in Part B. 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 in Part B.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no hypothese testing. Part B data will be only descriptively summarized.

5.2. 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), geometric mean (GM), geometric mean ratio (GMR) will also be included, where appropriate. Graphics may be used to present the data.

5.3. Methods to Manage Missing Data

Missing values will not be imputed for safety, efficacy and PK endpoints. 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.

6. ANALYSES AND SUMMARIES

Data will be summarized by treatment group. Efficacy analyses will be based on FAS, safety analyses will be based on the SAS, and PK analyses will be based on the PKAS. Demographics and baseline characteristics will be summarized for the SAS.

6.1. Primary Endpoint(s)

The primary endpoint is the change in magnitude of IL-2 response pre-and post-GC in peripheral blood from baseline (run-in) to Day 15. Data will be descriptively summarized by treatment group with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, max, GM/GMR for FAS using estimand 1 (Section 2.2.1, Section 5.2).

6.2. Secondary Endpoints

6.2.1. 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. Individual subject plasma concentration-time data will be plotted as well.

6.2.2. PK Parameters

PK parameters listed in Section 3.2 (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}.

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

See safety Section 6.6.1.

6.3. Exploratory Endpoints

6.3.1. PK Parameters

Exploratory PK parameters will not be measured/reported due to study termination.

6.3.2. 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 SAS.

6.3.3. Change in Magnitude of IL-2 Response pre- and post-GC in Peripheral Blood from Baseline to GC at Weeks 12, 24, and 36

These endpoints will not be measured/reported due to study termination.

6.3.4. Change in Magnitude of IL-2 Response pre- and post-GC in Peripheral Blood from GC at Day 15 to GC at Weeks 12, 24, and 36

These endpoints will not be measured/reported due to study termination.

6.3.5. Change in circulating levels of various biomarkers from pre-dose to post-dose on Day 1, 4, and 7

These endpoints will not be measured/reported due to study termination**.**

6.3.6. PROs

PRO endpoints will not be measured/reported due to study termination.

6.3.7. Biopsy Substudy

Biopsy substudy endpoints will not be measured/reported due to study termination.

6.4. Subset Analyses

N/A

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics listed in Section 3.4 will be summarized according to Sponsor's reporting standards for SAS.

6.5.2. Study Conduct and Subject Disposition

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

6.5.3. Study Treatment Exposure

The exposure to study drug will be summarized by treatment group for number of dosess of study intervention applied and number and percentage of participants who are compliant with the dosing regimen for SAS. A participant is considered compliant with the dosing regimen if he/she receives 80% to 120% of the expected amount of study intervention, in accordance with the protocol.

6.5.4. Gluten Challenge

GC will be summarized by number and percentage of participants completed GC at each GC scheduled timepoint for SAS.

6.5.5. 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.

6.6. 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.

6.6.1. Adverse Events

Adverse events will be summarized for 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.

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.

6.6.2. Safety laboratory Data

Clinical safety laboratory values and change from baseline and clinical significant change will be summarized according to Sponsor's standards.

6.6.3. Vital Signs

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

7. INTERIM ANALYSES

No interim analysis is planned for Part B. DSMB will review unblinded safety and PK data periodically and make recommendations for study continuation as defined in the DSMB charter.

8. REFERENCES

1. Protocol KAN-101-02.

APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change from baseline to Day 15 in IL-2 response	Summary	FAS	Observed cases, no imputation for missing data.	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. If two observations equally closet to the targeted day, the later will be used. 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	Day 8 – Day 21
Week 4	Day 28	Day 22 – Day 56
Week 12	Day 84	Day 57 – Day 126
Week 24	Day 168	Day 127 – Day 210
Week 36	Day 252	Day 211 – Day 308
Week 52	Day 365	Day 309 – 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 and including first dosing date
Day 4	Day 4 pre-dosing	Day 2 - Day 4 pre-dosing
Day 7	Day 7 pre-dosing	Day 5 - Day 7 pre-dosing
Day 15	Day 15 pre-GC	Day 8 - Day 15 pre-GC
Day 28	Day 28 pre-GC	Day 16 – Day 28 pre-GC
Week 12	Day 84 pre-GC	Day 29 – Week 12 pre-GC
Week 24	Day 168 pre-GC	Week 12 GC +1 day – Week 24 pre-GC
Week 36	Day 252 pre-GC	Week 24 GC +1 day – Week 36 pre-GC
Week 52	Day 364	Week 36 GC +1 day – 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 and including first dosing date
Day 4	Day 4 pre-dosing	Day 2 - Day 4 pre-dosing

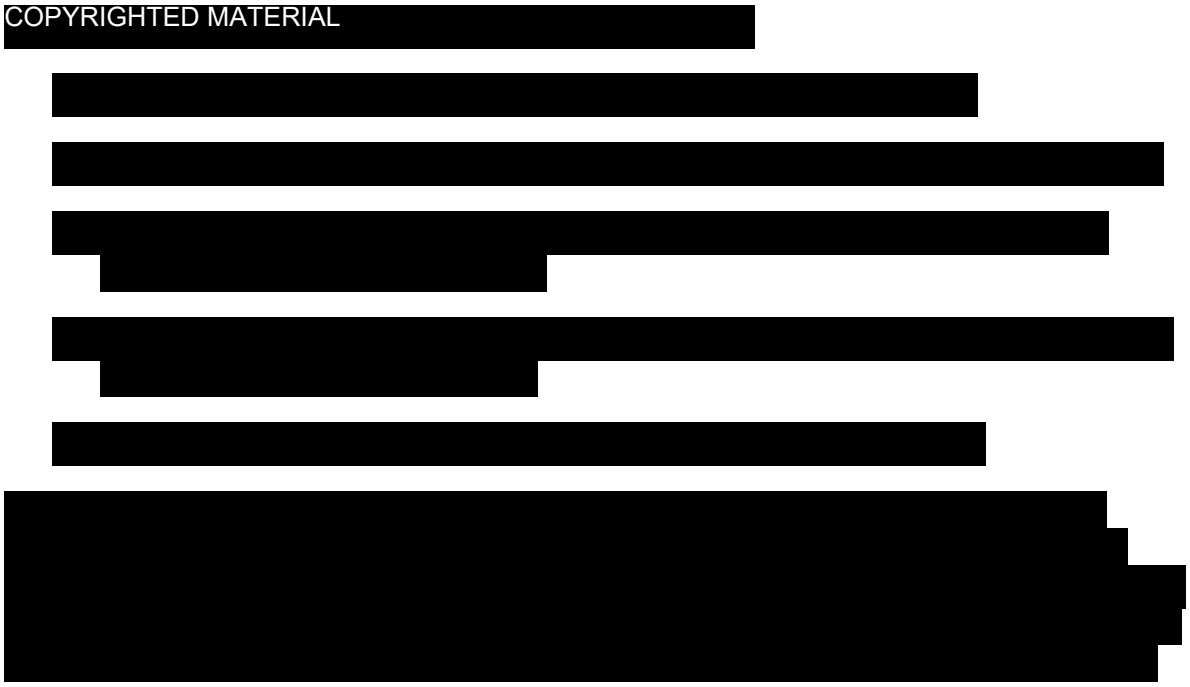
Table 5. Analysis Windows for Laboratory Tests

Visit Label	Targeted Day	Analysis window for data sets
Day 7	Day 7 pre-dosing	Day 5 - Day 7 pre-dosing
Day 15	Day 15 pre-GC	Day 8 - Day 15 pre-GC
Week 12	Day 84 pre-GC	Day 16 – Week 12 pre-GC
Week 24	Day 168 pre-GC	Week 12 GC + 1 day – Week 24 pre-GC
Week 36	Day 252 pre-GC	Week 24 GC + 1 day – Week 36 pre-GC
Week 52	Day 364	Week 36 GC + 1 day – end of study

Table 6. Analysis for Immunogenicity

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
Week 4	Day 28	Day 8 – Day 56
Week 12	Day 84	Day 57 – Day 126
Week 24	Day 168	Day 127 – Day 210
Week 36	Day 252 pre-GC	Day 211 – Day 308
Week 52	Day 364	Day 309 – enod of srudy

Appendix 2.2. Celiac Disease Symptom Diary (CDSD)



Appendix 2.3. Patient Global Impression of Severity (PGIS)

Appendix 2.4. Patient Global Impression of Change (PGIC)

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf} (dn)	dose normalized AUC_{inf}
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})
AUC_{last} (dn)	dose normalized AUC_{last}
BP	blood pressure
CDSD	celiac disease symptom diary
CeD	celiac disease
CL	apparent systemic clearance
C_{max}	maximum observed concentration
C_{max} (dn)	dose normalized C_{max}
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
min	minimum
max	maximum
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
V	apparent volume of distribution

Protocol KAN-101-02

A PHASE 1B OPEN-LABEL/ PHASE 2 DOUBLE-BLIND PLACEBO-CONTROLLED STUDY FOR PHARMACODYNAMIC ACTIVITY, SAFETY AND TOLERABILITY OF KAN-101 IN PATIENTS WITH CELIAC DISEASE

Part C

Statistical Analysis Plan
(SAP)

Version: 4

Date: 13Jun2025

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study KAN-101-02 Part C is based on the protocol amendment dated 30Jan2024.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 28Feb2024	Amendment 3 30Jan2024	Not Applicable (N/A)	N/A
2 05SEP2024	Amendment 3 30Jan2024	Added summary and analysis for Nausea Score and Vomiting Frequency and change from baseline	Sections 3.3 and 6.5.4.1, 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.
3 13DEC2024	Amendment 3 30Jan2024	Made clarification for baseline, 3-day and weekly average calculation and timepoints. Marsh score is categorical	Sections 3.3 and 6.4.5.1, CDSD average score calculation and analysis timepoint were updated. Section 6.4.6.1, Screening and Week 52 Marsh score will be summarized with frequency and percentage. Change from screening to Week 52 will be summarized using shift table

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
		Define IL-2 and CDSD analysis window	Appendix 2.1, Table 7 was added for IL-2 and CDSD analysis window.
4 13Jun2025	Amendment 3 30Jan2024	Study termination	Sections 6.3.1, 6.3.3, 6.3.4 and 6.3.5, 6.3.7 exploratory endpoints and biopsy substudy endpoints will not be measured/reported. Section 6.3.6, descriptive summary for PRO endpoints will be performed for data up to Week 12.

2. INTRODUCTION

Study KAN-101-02 is a 3-part, multicenter Phase 1b/2 study of KAN-101 in participants with celiac disease (CeD) on gluten-free diet (GFD). The 3 parts include: Part A – Open-label, multiple ascending dose (MAD); Part B – Double-blind, placebo (PBO)-controlled, parallel design (participants have baseline gluten change at Day -21); Part C – Double-blind, PBO-controlled, parallel design (there is no baseline gluten change).

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study KAN-101-02 Part C. As the populations for Part B and Part C are different (Part B participants have to demonstrate a symptomatic response following a 1-day oral GC performed during Run-in. There is no such requirement for Part C). Part B and Part C data will not be combined for analysis. 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.

2.1. Modifications to the Analysis Plan Described in the Protocol

"Entered" analysis set is added to Section 4, it is not in the protocol. The definition of "Enrolled" analysis set is different from that in the protocol.

2.2. Study Objectives, Endpoints, and Estimands

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

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:		
• Compare change in biomarker (IL-2) response following GC in participants with CeD treated with KAN-101 versus PBO.	• Change in levels of IL-2 from pre-GC to post-GC on Day 15.	• Estimand 2: a hypothetical estimand;
Secondary:		
• Assess the pharmacokinetics (PK) of multiple doses of KAN-101 in participants with CeD.	• KAN-101 plasma exposure as data permit: AUCinf, AUClast, Cmax, Tmax and t½.	• N/A.
• 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).	

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Tertiary/Exploratory:		
• To further characterize the PK profile of KAN-101 following multiple doses in participants with CeD.	• KAN-101 PK parameters, as data permit: AUCinf (dn), AUClast (dn), Cmax(dn), CL, V.	• N/A.
• To evaluate the immunogenicity of KAN-101.	• Incidence of development of anti-drug antibodies (ADA) during the study.	
• Assess the incidence of CeD symptoms in participants with CeD.	• Incidence of CeD symptoms as assessed by Patient Reported Outcomes (PROs) including: celiac disease symptom diary (CDSD) v2.1, patient global impression of change (PGIC) and patient global impression of severity (PGIS).	
• Compare change in biomarker response in participants with CeD and treated with KAN-101 versus PBO.	• Change in circulating levels of IL-2 from pre-GC to and post-GC at Weeks 12, 24, and 36.	
• Assess durability of biomarker (IL-2) response in peripheral blood of participants with CeD and treated with KAN-101 versus PBO.	• Change in circulating levels of various biomarkers from pre-dose to post-dose on Day 1, 4, and 7 (This analysis will be performed separately, not be included in the CSR). • Change in circulating levels of IL-2 pre- and post-GC in peripheral blood from Day 15 to Weeks 12, 24, and 36.	
Biopsy Substudy: • To evaluate the impact of KAN-101 on histology from esophagoduodenoscopy (EGD) biopsy in participants with CeD.	**Biopsy Substudy:** • Change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52.	
• Evaluate the potential relationship between histopathological state and response to 1 day GC	• Correlation between histological state, symptomatic response and biomarker responses (IL-2). (This analysis will be performed separately, not be included in the CSR)	

2.2.1. Primary Estimand

Estimand 2: The primary estimand is hypothetical, which estimates the treatment effect of KAN-101 vs PBO for IL-2 under the scenario of no intercurrent events. It includes the following 5 attributes:

- Population: Participant with CeD as defined by the Part C inclusion and exclusion criteria.
- Variable: log transformed IL-2 change from pre-GC to post-GC at Day 15.
- Treatment conditions: 3 dose groups of KAN-101 or PBO.
- Intercurrent Events: Prohibited medication, incomplete GC on Day 15, and discontinuation of study intervention. All data collected after any intercurrent events will be excluded.
- Population level summary: The LSM difference of the change from pre-GC to post-GC (log transformed) between each KAN-101 group and PBO.

2.2.2. Secondary Estimand

Estimand 3: This is a treatment policy estimand, which estimates the treatment effect of KAN-101 compared with PBO without regard to intercurrent events. It includes the following 5 attributes:

- Population: Participant with celiac disease as defined by the Part C inclusion and exclusion criteria.
- Variable: log transformed IL-2 change from pre-GC to post-GC at Day 15.
- Treatment condition: 3 dose groups of KAN-101 or PBO;
- Intercurrent event: intercurrent events will not be considered for analysis.
- Population-level summary: the LSM difference of the change from pre-GC to post-GC (log transformed) between each KAN-101 group vs PBO.

Estimand 3 will be used as a sensitivity analysis for the primary endpoint in Part C.

2.3. Study Design

Study KAN-101-02 is a 3-part, multicenter Phase 1b/2 study of KAN-101 in participants with CeD on GFD. The 3 parts include:

- **Part A** – Open-label, multiple ascending dose
- **Part B** – Double-blind, PBO-controlled, parallel design

- **Part C** – Double-blind, PBO-controlled, parallel design

Part C is a Phase 2, double-blind, PBO-controlled, parallel design study to compare the biomarker response (plasma IL-2; primary endpoint) following GC on Day 15. Safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years inclusive) with histology-confirmed CeD will also be evaluated.

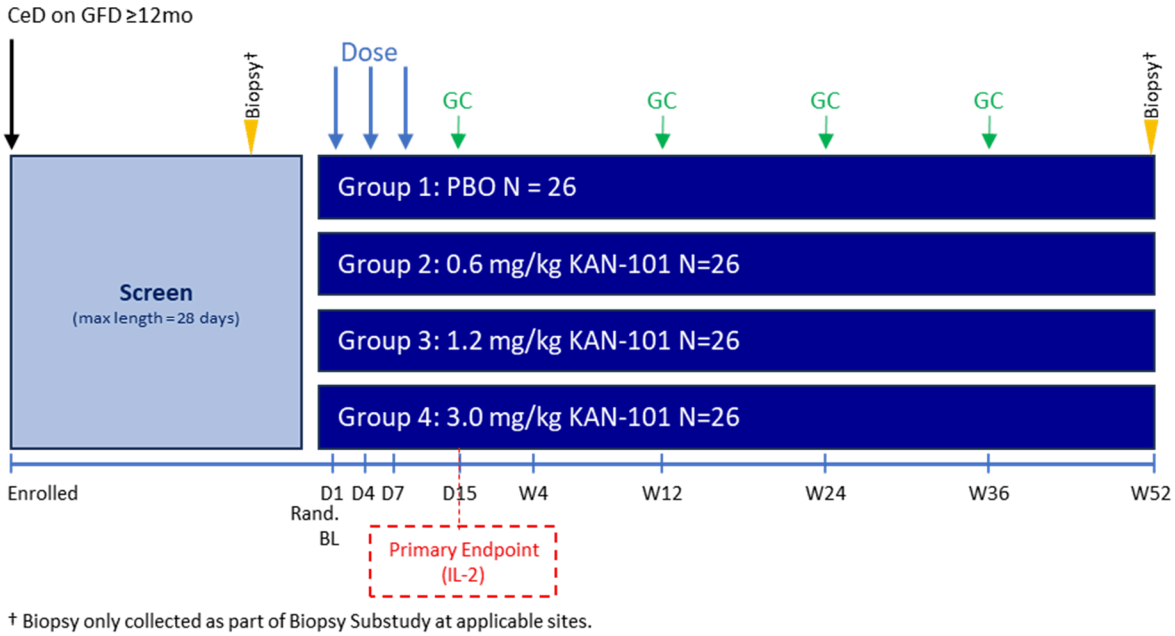
Eligible participants will be randomized 1:1:1:1 and stratified by participation in biopsy substudy to one of the following 4 treatment groups and administered study intervention IV for 3 administrations (1 administration every 3 days starting at Day 1):

- PBO (Group 1)
- 0.6 mg/kg (Group 2)
- 1.2 mg/kg (Group 3)
- 3.0 mg/kg (Group 4)

All participants will return to the clinic at Day 15, Weeks 12, 24, and 36 to receive a 1-day 9 g oral GC to assess plasma IL-2 biomarker response to gluten and collect symptom information and follow-up visits on Day 28 and Week 52.

Participants participating biopsy substudy at applicable sites will receive biopsies at screening and Week 52.

Figure 1. Part C Study Design Schema



† Biopsy only collected as part of Biopsy Substudy at applicable sites.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- Change in IL-2 from pre-GC to post-GC on Day 15 (log transformed IL-2 values will be used in analysis model). .

3.2. Secondary Endpoints

- KAN-101 plasma exposure as data permit: 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 (Clast)	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	AUC_{last} + (Clast/K_{el}), where Clast is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time to first occurrence of C_{max}	
$t_{½}$[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.

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

See Section 3.5.1.

3.3. Exploratory Endpoints

- KAN-101 PK parameters, as data permit: AUC_{last}(dn), AUC_{inf}(dn), C_{max}(dn), CL, V.

Parameter	Definition	Method of Determination
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}(dn)	Dose normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}(dn)	Dose normalized C_{max}	C_{max}/Dose
CL[a]	Apparent systemic clearance	Dose/AUC_{last}
V[a]	Apparent volume of distribution following IV dosing	Dose/AUC_{inf}×K_{el}

a. If data permits.

- Incidence of development of ADA during the study

  Positive of ADA will be assessed at Days 1, 7, 28, Weeks 12, 24, 36, 52 or early termination (ET) visit.

- The observed value and the change in CDSD

  CDSD is a patient reported outcome (PRO) questionnaire. The version 2.1 includes 5 severity items and 3 frequency supplement questions (see Appendix 2.2) that will be collected daily. Each individual item and question as well as the CDSD Total Score (calculation found in Appendix 2.2), CDSD GI Score will be summarized and analyzed for weekly average at weeks 3, 12, 24, 36, as well as for daily assessment at GC Day 15, and Weeks 12, 24, 36 GC. Baseline CDSD is the average of most recent 7-day interval scoresbefore Day 1 (not include Day 1) with at least 4 days with non-missing scores. If there are ≥4 days missing scores within any 7-day interval before Day 1, the baseline is set as missing. 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. Weeks 3, 12, 24, 36 average will be calculated. The start day for each week is the GC day at the related time point (see Table 7).

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

- The change from baseline in CDSD Nausea score and vomiting frequency for Day 15, Week 12, Week 24 and Week 36 will be calculated as a 1 day, 3-day average, and 7-day average (weekly average) score. The start day for 1-day, weekly and 3-day interval is the GC day at the related time point (see Table 7). If daily scores are missing for more than half of total days in a specific week or the score on GC day is missing, the average score is set as missing for that week. If ≥2 observations are missing for a 3-day interval, the 3-day average score will not be calculated. If the score is missing on the GC day, the 3-day and 7-day average at that time point are set as missing as well. The baseline as dercribed in previous paragraph will be used as the baseline to calculate the change from the 1-day, 3-day and 7-day score.

- 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, 28, Weeks 12, 24, 36, 52, 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, 28, Weeks 12, 24, 36, 52, or ET visit.

- The observed value and the change in IL-2 from pre-GC to post-GC at Weeks 12, 24, and 36 (log transformed IL-2 will be used in analysis model).

- The observed value and the change in circulating levels of IL-2 pre- and post-GC from Day 15 to Weeks 12, 24, and 36.

  The change from Day 15 in circulating levels of IL-2 to Weeks 12, 24, or 36 is (post-GC IL-2 at each week – pre-GC IL-2 at each week) – (post-GC IL-2 at Day 15 – pre-GC IL-2 at Day 15). For analysis, log transformed IL-2 will be used.

- The observed value and the change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52 for substudy.

3.4. 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)
- HLA genotype
- CeD Serology at diagnosis
- Histology at diagnosis
- PGIS
- CDSD total score

3.5. Safety Endpoints

Safety will be assessed by medical history, vital signs, clinical laboratory tests, and the spontaneous 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' well-being. All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations. All safety analyses will be performed on the safety population (See Section 6.6).

3.5.1. Adverse Events

Incidence and severity of TEAEs is the Secondary endpoint of Part C.

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 (V5.0) 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.

3.5.2. Safety Laboratory Data

Safety laboratory testing will be performed at Screening, Days 1, 15, Weeks 12, 24, 36, 52, 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	Urea and creatinine 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 hsCRP	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] • Hepatitis B surface antigen and HbcAb. HBsAb and HBV DNA as reflex tests • Hepatitis C antibody and HCV RNA as reflex testHIV • HLA genotype and CeD serology (eg, HLA DQ2.5 and HLA DQ8 testing[d], tTG and DGP IgA/IgG[e])

a. Only if UTI 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.
e. For tTG, a result of <2 x ULN will be considered negative or weak positive. For DGP, a result of <30 U/mL will be considered negative or weak positive.

3.5.3. Vital Signs

Vital signs will be assessed at Screening, Days 1, 4, 7, 15, 28, Weeks 12, 24, 36, 52, or ET visit. On dosing days, orthostatic vital signs including SBP, DBP, and PR will be collected approximately 5 minutes pre-dose, and approximately 45 minutes, 2 hours, and then, every 2 hours until discharge, post dose.

4. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined for Part C:

Analysis Set	Description
Entered	All participants who sign the ICD.
Enrolled (Randomized or assigned to study intervention)	All entered participants who are randomized to study intervention in Part C.
Full analysis set (FAS)	All participants who are randomly assigned to study intervention and receive any portion of study intervention in Part C. Participants will be analyzed according to the intervention they are randomized.

Analysis Set	Description
Safety analysis set (SAS)	All participants who receive any portion of study intervention in Part C. 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 in Part C.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This protocol Part C is designed to establish the superiority of 3 doses of KAN-101 to PBO for the primary endpoint the change in IL-2 from pre-GC to post-GC at Day 15. The null hypothesis is that there is no difference between any dose of KAN-101 and PBO, and the alternative hypothesis is that there is a significant difference between at least one dose of KAN-101 and PBO. KAN-101 will be considered superior to PBO with respect to IL-2 response if the difference is statistically significant at the 2-sided 0.05 level. There is no adjustment for multiplicity.

5.2. 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 may be used to present the data.

5.2.1. Analyses for Continuous Endpoints

For continuous endpoints in Part C, 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 each dose group of KAN-101 to PBO (providing LSM of the treatments, LSM of the treatment difference, p-value and 95% CI) will be generated.

5.3. Methods to Manage Missing Data

Missing values will not be imputed for safety, efficacy and PK endpoints. 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.

6. ANALYSES AND SUMMARIES

Data will be summarized by treatment group. Efficacy analyses will be based on FAS, safety analyses will be based on the SAS, and PK analyses will be based on the PKAS. Demographics and baseline characteristics will be summarized for the SAS.

6.1. Primary Endpoint(s)

The primary endpoint is IL-2 change from pre-GC to post-GC on Day 15.

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

Log transformed IL-2 will be used in statistical analysis models (log transform each individual IL-2 value first, then calculate the change).

6.1.1. Main Analysis

- Estimand strategy: Hypothetical estimand, Estimand 2 (Section 2.2.1).
- Analysis set: FAS (Section 4).
- Variable: log transformed IL-2 change from pre-GC to post-GC on Day 15.
- Analysis method: ANCOVA model (Section 5.2.1).
- Intercurrent event: Prohibited medication, incomplete GC on Day 15, and discontinuation of study intervention. All data collected after any intercurrent events will be excluded. Missing values will not be imputed.
- The LSM change from pre-GC to post-GC (log transformed), LSM difference of the change between each KAN-101 group and PBO, 95% CI, and p-value will be presented. Exponentially transformed values for LSM, LSM difference, 95% CI will be presented as well.

Note: based on the population attribute of Estimand 2, participants who didn't meet the HLA inclusion criteria will be excluded from the analysis.

6.1.2. Sensitivity Analysis

- Estimand strategy: Treatment policy estimand, Estimand 3 (Section 2.2.2)
- Analysis set: FAS (Section 4)
- Variable: log transformed IL-2 change from pre-GC to post-GC on Day 15.
- Analysis method: ANCOVA in Section 5.2.1
- Intercurrent event: intercurrent events will not be considered for analysis. Missing values will not be imputed.
- The LSM change from pre-GC to post-GC (log transformed), LSM difference of the change between each KAN-101 group and PBO, 95% CI, and p-value will be

presented. Exponentially transformed values for LSM, LSM difference, 95% CI will be presented as well.

Note: based on the population attribute of Estimand 3, participants who didn't meet the HLA inclusion criteria will be excluded from the analysis.

6.2. Secondary Endpoints

6.2.1. 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. Individual subject plasma concentration-time data will be plotted as well.

6.2.2. PK Parameters

PK parameters listed in Section 3.2 (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}.

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

See safety Section 6.6.1.

6.3. Exploratory Endpoints

6.3.1. PK Parameters

Exploratory PK parameters will not be measured/reported due to study termination.

6.3.2. 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 SAS.

6.3.3. Change in circulating levels of IL-2 from pre-GC to and post-GC at Weeks 12, 24, and 36

These endpoints will not be measured/reported due to study termination.

6.3.4. Change in Circulating Levels of IL-2 Response pre- and post-GC in Peripheral Blood from GC at Day 15 to GC at Weeks 12, 24, and 36

These endpoints will not be measured/reported due to study termination.

6.3.5. Change in circulating levels of various biomarkers from pre-dose to post-dose on Day 1, 4, and 7

These endpoints will not be measured/reported due to study termination.

6.3.6. PROs

6.3.6.1. CDSD

Weekly scores for each item and question of the CDSD as well as the CDSD Total Score, CDSD Gastrointestinal (GI) Score (see Section 3.3 and Appendix 2.2) and change from baseline will be descriptively summarized with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, max for each treatment group by timepoint. The change from baseline will be analyzed using ANCOVA models in Section 5.2.1 by timepoint. LSM of the treatments, LSM of the treatment difference with PBO, p-value and 95% CI will be generated. The summary and analysis will be performed for weekly average at weeks 3, 12, 24, 36, as well as for daily assessment at GC Day 15, and Weeks 12, 24, 36 GC. 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 or the score on GC day is missing, the average score is set as missing for that week.

The change from baseline in CDSD Nausea score and vomiting frequency for Day 15, Week 12, Week 24 and Week 36 GC will be evaluated as a 1-day, 3-day and 7-day score, summarized as stated above, and analyzed within each KAN treatment, and combined, 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 each of KAN group.

Line plots by treatment group will be provided for mean (± SD).

Due to study termination, only descriptive summaries will be provided for data up to Week 12.

6.3.6.2. PGIS

PGIS and change from baseline will be descriptively summarized with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, max for each treatment group by timepoint. The change from baseline will be analyzed using ANCOVA models in Section 5.2.1 by timepoint. LSM of the treatments, LSM of the treatment difference with PBO, p-value and 95% CI will be generated.

Due to study termination, only descriptive summaries will be provided for data up to Week 12.

6.3.6.3. PGIC

PGIC will be descriptively summarized with number of observations, mean, SD, min, 1st, 2nd and 3rd quartiles, max for each treatment group by timepoint. PGIC will be analyzed using ANOVA models in Section 5.2.1 by timepoint. LSM of the treatments, LSM of the treatment difference with PBO, p-value and 95% CI will be generated.

Due to study termination, only descriptive summaries will be provided for data up to Week 12.

6.3.7. Biopsy Substudy

Biopsy substudy endpoints will not be measured/reported due to study termination.

6.4. Subset Analyses

N/A

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics listed in Section 3.4 will be summarized according to Sponsor's reporting standards for SAS.

6.5.2. Study Conduct and Subject Disposition

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

6.5.3. Study Treatment Exposure

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

6.5.4. Gluten Challenge

GC will be summarized by number and percentage of participants completed GC at each GC scheduled timepoint for SAS.

6.5.5. 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.

6.6. 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.

6.6.1. Adverse Events

Adverse events will be summarized for 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.

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.

6.6.2. Safety Laboratory Data

Clinical safety laboratory values and change from baseline and clinical significant change will be summarized according to Sponsor's standards.

6.6.3. Vital Signs

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

7. INTERIM ANALYSES

An interim analysis (IA) may be conducted and results may be used to inform internal decisions regarding future study planning.

Before any IA is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per the sponsor's SOPs will be documented and approved in a DSMB charter.

In addition, DSMB will review unblinded safety and PK data periodically and make recommendations for study continuation as defined in the DSMB charter.

8. REFERENCES

1. Protocol KAN-101-02.

APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Change in IL-2 from pre-GC to post-GC at Day 15	Summary	FAS	Observed cases, no imputation for missing data.	N/A
	Main analysis	FAS	Data collected after intercurrent events will be excluded. Missing data will not be imputed.	ANCOVA with terms treatment, pre-GC IL-2 at Day 15
	Sensitivity/supplementary analysis	FAS	All data collected will be included regardless of intercurrent events. Missing data will not be imputed.	ANCOVA with terms treatment, pre-GC IL-2 at Day 15
CDSD (Each item and question of the CDSD as well as the CDSD Total Score, CDSD Gastrointestinal (GI) Score) change from baseline at each timepoint	Summary	FAS	Observed cases, no imputation for missing data.	N/A
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, no imputation for missing data.	N/A

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
PGIS change from baseline at each timepoint	Summary	FAS	Observed cases, no imputation for missing data.	N/A
PGIC at each timepoint	Summary	FAS	Observed cases, no imputation for missing data.	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. If two observations are equally close to the targeted day, the later will be used. 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	Day 8 – Day 21
Week 4	Day 28	Day 22 – Day 56
Week 12	Day 84	Day 57 – Day 126
Week 24	Day 168	Day 127 – Day 210
Week 36	Day 252	Day 211 – Day 308
Week 52	Day 365	Day 309 – 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 and including first dosing date
Day 4	Day 4 pre-dosing	Day 2 - Day 4 pre-dosing
Day 7	Day 7 pre-dosing	Day 5 - Day 7 pre-dosing
Day 15	Day 15 pre-GC	Day 8 - Day 15 pre-GC
Day 28	Day 28 pre-GC	Day 16 – Day 28 pre-GC
Week 12	Day 84 pre-GC	Day 29 – Week 12 pre-GC
Week 24	Day 168 pre-GC	Week 12 GC +1 day – Week 24 pre-GC
Week 36	Day 252 pre-GC	Week 24 GC +1 day – Week 36 pre-GC
Week 52	Day 364	Week 36 GC +1 day – 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 and including first dosing date
Day 4	Day 4 pre-dosing	Day 2 - Day 4 pre-dosing

Table 5. Analysis Windows for Laboratory Tests

Visit Label	Targeted Day	Analysis window for data sets
Day 7	Day 7 pre-dosing	Day 5 - Day 7 pre-dosing
Day 15	Day 15 pre-GC	Day 8 - Day 15 pre-GC
Week 12	Day 84 pre-GC	Day 16 – Week 12 pre-GC
Week 24	Day 168 pre-GC	Week 12 GC + 1 day – Week 24 pre-GC
Week 36	Day 252 pre-GC	Week 24 GC + 1 day – Week 36 pre-GC
Week 52	Day 364	Week 36 GC + 1 day – end of study

Table 6. Analysis for Immunogenicity

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
Week 4	Day 28	Day 8 – Day 56
Week 12	Day 84	Day 57 – Day 126
Week 24	Day 168	Day 127 – Day 210
Week 36	Day 252 pre-GC	Day 211 – Day 308
Week 52	Day 364	Day 309 – enod of srudy

Table 7. Analysis for IL-2 and CDSD (GC day at each time point)

Visit Label	Targeted Day	Analysis window for data sets
Day 15	Day 15	Day 14 -Day 16
Week 12	Day 84	Day 70 - Day 98
Week 24	Day 168	Day 154 – Day 182
Week 36	Day 252	Day 238 – Day 266

Appendix 2.2. Celiac Disease Symptom Diary (CDSD)

Appendix 2.3. Patient Global Impression of Severity (PGIS)

Appendix 2.4. Patient Global Impression of Change (PGIC)

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	Analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf} (dn)	dose normalized AUC_{inf}
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})
AUC_{last} (dn)	dose normalized AUC_{last}
BP	blood pressure
CDSD	celiac disease symptom diary
CeD	celiac disease
CL	apparent systemic clearance
C_{max}	maximum observed concentration
C_{max} (dn)	dose normalized C_{max}
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
min	minimum
max	maximum
N/A	not applicable
PBO	placebo

Abbreviation	Term
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
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
V	apparent volume of distribution