STUDY PROTOCOL

KAN-101-01

A Phase 1 Study of the Safety and Tolerability of Single and Multiple Doses of KAN-101 in Patients with Celiac Disease

Protocol Number:	KAN-101-01
Phase:	1
Date of Protocol:	29 March 2021
Version:	Version 7
IND:	19492
Sponsor:	Kanyos Bio, Inc. a wholly owned subsidiary of Anokion S.A. 50 Hampshire St. Cambridge, MA 02139

INVESTIGATOR APPROVAL

I have read both the KAN-101 Investigator's Brochure and Protocol KAN-101-01 and agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice (GCP) and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (dd/mm/yyyy): _____

PPD

[redacted]

CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Title of Study

A Phase 1 Study of the Safety and Tolerability of Single and Multiple Doses of KAN-101 in Patients with Celiac Disease

Name of Investigational Product

KAN-101

Name of Active Ingredient

CCI [redacted]

Study Center(s)

Approximately 5 to 12 sites in the United States

Study Period (Years)	**Phase of Development**
Estimated date first patient enrolled: January 2020 Estimated date last patient completed: June 2021	1

Objectives

- Primary (Part A and Part B)
  - Assess the safety and tolerability of escalating doses of KAN-101 in patients with celiac disease (CeD)
- Secondary (Part A and Part B)
  - Assess the pharmacokinetics (PK) of KAN-101 after single and multiple doses of KAN-101 in patients with CeD
- Exploratory (Part B only)
  - Examine the magnitude of the biomarker responses in peripheral blood following gluten challenge (GC)
  - Assess the incidence of CeD symptoms after a GC

Methodology

This is a two-part, multicenter Phase 1 study of KAN-101 in patients with CeD.

The 2 parts include:

- Part A – First-in-human (FIH) single ascending dose (SAD)

- Part B – Randomized, placebo (PBO)-controlled, double-blind, multiple ascending dose (MAD)

The study will be conducted in adult patients (≥ 18 years) diagnosed with CeD as demonstrated by intestinal histology and positive serology at the time of diagnosis, who have been following a gluten-free diet (GFD) for > 12 months. Eligible patients must have Human Leukocyte Antigen HLA-DQ2.5 genotype (*HLA-DQA1*05* and *HLA-DQB1*02*) (homozygotes or heterozygotes) since the KAN0009 peptide binds to this major histocompatibility complex (MHC) molecule; patients positive for HLA-DQ8 (*DQA1*03, DQB1*0302*) will be excluded, since the KAN0009 peptide does not bind to this MHC molecule.

Part A – SAD

Part A employs a SAD 3+3 design, in which patients will receive a single IV infusion of KAN-101 on Day 1 (D1) followed by 20 days of safety monitoring, which includes assessment of adverse events (AEs), clinical signs and symptoms, and clinical laboratory values.

All cohorts in Part A will employ sentinel dosing, whereby the first patient in each cohort will be dosed at least 7 days prior to the subsequent patients to monitor for the acute and subacute safety of KAN-101.

The doses for Part A include 0.15 mg/kg (Cohort 1), 0.3 mg/kg (Cohort 2), 0.6 mg/kg (Cohort 3), and 1.2 mg/kg (Cohort 4). After the last patient within a given dose cohort has been followed for at least 7 days post-dose, a safety review will be performed by the SMC and will include review of all available safety and PK information. Dosing at the next dose level will only commence upon a recommendation from the SMC and agreement by the Sponsor.

For all patients in Part A, the study will consist of a 28-day screening period, a single dose of KAN-101 administered on D1 followed by a 10-hour monitoring period in the clinic/hospital unit. Patients will be evaluated on D4 (±1), D8, and D21. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the trial participant where appropriate. Blood and serum samples will be collected for PK and ADA assessments during the Part A.

Please see Table 1 for the complete schedule of assessments for Part A.

Part B - MAD

Patients enrolled in the double-blind MAD part will be randomized 3:1 to KAN-101 or PBO administered IV for 3 doses. A total of 8 patients per dose cohort (6 KAN-101; 2 PBO) will be enrolled. All cohorts will employ sentinel dosing, whereby the first 2 patients (1 KAN-101 and 1 PBO) in each cohort will be dosed at least 14 days prior (ie, 7 days from third and final dose) to the subsequent patients being dosed to monitor for the acute and subacute safety of multiple doses of KAN-101.

The first MAD cohort (Cohort 5) will begin dosing after the safety review of the SAD Cohort 2 is completed. In Part B, the doses will be administered every 3 days, for a total of 3 doses, and the patients followed for approximately 28 days after the first dose. The planned Part B doses are 0.15 mg/kg, 0.3 mg/kg, and 0.6 mg/kg.

For all cohorts in Part B, after the last patient dosed within a given cohort has been followed for at least 14 days, a safety review will be performed by the SMC. Dosing in the next cohort will commence upon recommendation by the SMC and approval by the Sponsor.

A GC will be initiated on D15 to assess patients' T-cell response to gluten. For the GC, patients will self-administer 9 g of gluten protein orally (PO) on D15, D16, and D17, at approximately the same time each day. CCI [redacted].

For all patients in Part B, the study will consist of a screening period of up to 28 days, followed by 3 doses of KAN-101 or PBO administered on D1, D4, and D7. The first dose on D1 is followed by a 10-hour monitoring period in the clinic/hospital unit, after which patients will return home before returning on D4 and D7 for the second and third doses, respectively. The D4 and D7 doses will be followed by a 4-hour monitoring period in the clinic. Patients will return to the clinic on D15 to initiate GC and D21 for biomarker sample collection. Patients will have a follow-up phone call on D28. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the trial participant where appropriate.

Based on data obtained during both the SAD and MAD parts of the study, the protocol may be amended to explore additional dose levels and dosing schedules if supported by the data and recommended by the SMC and approved by the Sponsor.

Please see Table 2 for the complete schedule of assessments for Part B.

Number of Patients (Planned)

It is anticipated that the study will enroll approximately 36 patients. Part A (SAD) will enroll approximately 12 to 24 patients using a 3+3 dose escalation design without intra-patient dose escalation. Part B (MAD) will enroll approximately 24 patients across 3 dose cohorts (6 active patients per cohort). A sample size of 6 patients treated with KAN-101 per cohort in Part B allows for an 0.80 power to detect a treatment-related AE occurring at an event rate of 0.25.

In Part A, patients may be replaced if they do not receive the full dose of study drug or do not complete the D8 visit, as long as they did not discontinue the study due to an AE assessed as related to KAN-101. In Part B, patients may be replaced if they do not receive the full 3 doses of study drug or do not complete the D21 visit, as long as they did not discontinue the study due to a DLT assessed as related to KAN-101.

Starting Dose and Dose Escalation

The initial starting dose of KAN-101 in the Protocol version 2.0 was 1.5 mg/kg, a dose level consistent with an expected efficacious dose and supported by findings from the Good Laboratory Practice (GLP) toxicology studies. Due to non-serious adverse events observed in one patient at the 1.5 mg/kg dose level, the protocol has been amended to start at the dose of 0.15 mg/kg, 10-fold lower than the dose which induced symptoms consistent with gluten ingestion in celiac patients.

Part A will use a 3+3 design to evaluate escalating single doses of KAN-101. Approximately 12 to 24 patients are anticipated for enrollment in Part A. At any dose level, if none of the first 3 patients experiences a dose-limiting toxicity (DLT) (defined as any ≥ Grade 3 AE assessed as related to KAN-101 or any Grade 2 AE assessed as related to KAN-101 not resolving within 14 days) then escalation to the next dose level may proceed if recommended by the SMC and approved by the Sponsor. If 1 of the first 3 patients experiences a DLT, the dose level will expand to a maximum of 6 patients if recommended by the SMC. If no DLT occurs among the 3 additional patients enrolled at that dose level, then escalation to the next dose level may proceed if recommended by the SMC and approved by the Sponsor.

Any DLT experienced during the study will result in study pause and review by the SMC. Any ≥ Grade 4 AE will result in notification of the FDA in parallel with the SMC and study dosing and enrollment will be paused pending review by FDA. The non-tolerated dose (NTD) is the dose level at which 2 or more patients experience a DLT during the dose escalation safety monitoring period. The maximum tolerated dose (MTD) will be defined as the dose level immediately below the NTD. Of note, dose escalation may not identify an NTD or MTD.

Safety Monitoring Committee

This study will utilize an SMC that will meet regularly to review all accumulated data, including safety and PK (when available) during dose escalation. The SMC will recommend all dose escalation decisions, and/or any changes to the dosing paradigm based on review of the received data. The SMC will also make recommendations about the dose(s) selected for Part B. The Sponsor will make all final decisions related to the doses and regimens examined in this study.

Inclusion Criteria

1. Adults aged 18 to 70 years inclusive
2. Diagnosed with CeD based on positive serology (eg, tissue transglutaminase IgA antibody [tTG-IgA] and/or deamidated gliadin peptide IgG [DGP-IgG]) and intestinal histology consistent with ≥ Marsh Type II or with evidence of villous atrophy
3. Has HLA-DQ2.5 genotype (*HLA-DQA1*05* and *HLA-DQB1*02*) (homozygotes or heterozygotes)
4. Has followed a GFD for > 12 months immediately prior to study entry

5. Negative or weak positive for transglutaminase (tTG) IgA and negative or weak positive for DGP-IgA/IgG during screening
6. Male or female. Females of childbearing potential must use at least 2 acceptable birth control methods
7. Capable of understanding and complying with protocol requirements
8. Patient understands and has signed the informed consent form (ICF)

Exclusion Criteria

1. Refractory CeD
2. Selective IgA deficiency
3. Positive for HLA-DQ8 (*DQA1*03, DQB1*0302*)
4. Previous treatment with tolerance-inducing therapies for CeD
5. Known wheat allergy
6. **Part B only:** History of hyperacute (requiring medical treatment) or prolonged symptoms (> 48 hours) following gluten exposure
7. Has active inflammatory bowel disease (eg, Crohn's disease, colitis)
8. Presence of other autoimmune disorders in addition to CeD, including but not limited to type 1 diabetes, rheumatoid arthritis, psoriasis, autoimmune thyroid disease, etc.
9. Uncontrolled or significant medical conditions (including active infections or chronic hepatitis) which, in the opinion of the Investigator, preclude participation
10. Patients with clinical signs and symptoms consistent with COVID-19 (eg, fever, dry cough, dyspnea, sore throat, and fatigue) or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission

    Note: Patients who experienced symptoms consistent with COVID-19 or confirmed infection during the screening period (ie, after signing the ICF but before dosing) may be rescreened after 4 weeks
11. Patients with a prior severe course of COVID-19 requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation
12. Receipt of chronic, systemic non-biologic immunosuppressive or immunomodulatory therapies within the last 3 months (eg, methotrexate, sulfasalazine, or corticosteroids such as prednisone, etc.)
13. Positive for HIV, HBV, or HCV
14. Receipt of any vaccination within 4 weeks prior to first dose of study drug
15. Receipt of biologic immunosuppressive or immunomodulatory therapies within the last 12 months (eg, adalimumab, etanercept, certolizumab, etc.)
16. Has any of the following laboratory parameters at Screening:
    a. Hemoglobin < 10 g/dL

b. Platelet (PLT) count < 100 x 10^9/L
c. White blood cell count (WBC) outside the normal range and assessed as clinically significant by the Investigator
d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) > 1.5 x the upper limit of normal (ULN)
e. Estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2 based on the Cockcroft-Gault equation during screening

17. Average alcohol consumption of > 2 drink-equivalents per day
18. History of dermatitis herpetiformis
19. Pregnant or breastfeeding

Investigational Product, Dosage, and Mode of Administration

CCI [redacted]

Administration will be by IV infusion over approximately 30 minutes.

For Part A, patients will receive a single IV infusion of KAN-101.

For Part B, patients will receive a total of 3 IV infusions of either KAN-101 or PBO, with each of the doses administered on D1, D4, and D7. All doses will be prepared as outlined in the Pharmacy Manual by an unblinded pharmacist.

Study Duration

The maximum duration of study participation for patients in Part A is approximately 49 days, which includes a screening period of up to 28 days, followed by a single dose of KAN-101 on D1, and a 3-week follow-up period.

The maximum duration of study participation for patients in Part B is approximately 56 days, which includes a screening period of up to 28 days, followed by 3 doses of KAN-101 each administered on D1, D4, and D7, a GC on D15 to D17, assessment on D21, and a final phone call on D28.

Assessment of Safety

Safety will be assessed through the monitoring of AEs, clinical signs and symptoms, vital signs, and clinical laboratory evaluations.

Patients will be monitored continuously for AEs from screening until the final Safety Follow Up Visit on D21 (Part A) or final phone call on D28 (Part B). AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 or higher.

In relation to patient safety during the COVID-19 pandemic, current national laws and local recommendations should be strictly adhered to during the study.

Patient safety will be evaluated during Part A (SAD) and Part B (MAD) to determine dose escalation. The dose escalation safety monitoring period in Part A is from the single IV administration of KAN-101 through the D8 clinic visit. The dose escalation safety monitoring period in Part B is from the first IV administration of KAN-101 or PBO through the D15 clinic visit, prior to initiating the GC.

In both parts, patients will be monitored in the clinic for 10 hours following the first IV administration KAN-101 or PBO. In Part B patients will be monitored in the clinic for 4 hours following completion of the second and third IV infusion of KAN-101 or PBO.

Any DLT experienced during the dose escalation safety monitoring period will result in a pause in the study enrollment and a review of all the available safety data by the SMC prior to dosing any additional patients on either part of the study. Any ≥ Grade 4 AE will result in notification of the FDA in parallel with the SMC and study dosing and enrollment will be paused pending review by FDA.

Primary Endpoint (Part A and Part B)

- Incidence and severity of treatment-emergent AEs (TEAEs) as assessed by the CTCAE v5.0

Secondary Endpoint (Part A and Part B)

- Plasma concentrations and PK parameters of KAN-101

Exploratory Endpoints (Part B only)

CCI

Pharmacokinetics

In Part A and Part B, samples for PK assessment will be collected according to the schedules outlined in Table 1 and Table 2. Part A and Part B will be analyzed separately and together.

Statistical Methods

Statistical methods will be descriptive. No hypothesis will be formally tested. For Part A, the data will be listed by dose level. For Part B, summary statistics will be provided by dose level. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (n), mean, standard deviation (StD), median, and range (minimum and maximum).

Part A and Part B will be analyzed separately and together.

A formal statistical analysis plan (SAP) will be developed and finalized prior to study database lock.

Table 1: Schedule of Assessments Part A (SAD)

Assessment	Screening	Study Period				Early Term.
Study Day	**-28**	**1**	**4 (±1)**	**8**	**D21 (±1)**	
Screening Assessments						
Informed Consent	X					
Medical History & Demographics	X					
Disease History	X					
Inclusion/Exclusion	X					
ECG	X	X[2]		X		
HIV, HBV, HCV testing	X					
HLA Genotype and CeD Serology[1]	X					
Clinical Procedures						
Physical Examination	X[3]					X
Pregnancy Test[4]	X	X[5]				
Vital Signs[6]	X	X[5]		X		
Con Meds/Procedures, Incidental Gluten Exposure	X	X	X	X	X	X
Safety Assessments						
Adverse Events	X	X[7]	X	X	X	X
Lab Tests (Safety)	X	X[5]	X	X		X
Study Drug Administration						
KAN-101 Administration		X				
Additional Blood Samples						
PK Blood Sample		X[8]				
ADA Serum Sample		X[5]			X	X

[1] All patients will be assessed via central laboratory for HLA genotype and CeD serology (eg, tTG-IgA and DGP-IgG) at screening to confirm eligibility. For rescreening, HLA does not need to be repeated and CeD serology only needs to be repeated if >3months have elapsed from last assessment.

[2] ECG performed pre dose (at least 5 min before infusion), 20(±5) min after start of infusion, and 1 hour (±10 min) post infusion

[3] Includes weight and height at screening only.

[4] Pregnancy test at screening must be serum; serum or urine tests are acceptable on D1 prior to dosing. Pregnancy test must be negative before study drug is administered.

[5] Samples/Measurements taken pre-dose (at least 5 min prior to infusion).

[6] Vital signs (pulse rate, temperature, diastolic and systolic BP).

[7] On D1 patients will be observed in the clinic/hospital unit for 10 h after initiation of IV infusion and followed up with by phone approximately 24 hours after dosing.

[8] PK samples to be taken pre-dose (at least 5 min prior to infusion) and the following timepoints after the end of infusion: 0 (+2) min, 7 (±2) min, 15 (±2) min, 30 (±5) min, 1 h (±5 min), 2 h (±5 min), 3 h (±5 min), 4 h (±5 min) and 6 h (±5 min).

Abbreviations: ADA = anti-drug antibody; BB = blood pressure; CeD = celiac disease; Con Meds = concomitant medications; ECG = electrocardiogram; Early Term. = early termination; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; HLA = Human Leukocyte Antigen; PK = pharmacokinetics; SAD = single ascending dose.

Table 2: Schedule of Assessments Part B (MAD)

Assessments	Screening	Treatment Period			PD Assessment		Follow-up[1]	Early Term.
Study Day	**-28**	**1**	**4**	**7**	**15**	**21**	**28 (±3)**	
Screening Assessments								
Informed Consent	X							
Medical History & Demographics	X							
Disease History	X							
Inclusion/Exclusion	X							
ECG	X	X[2]		X[2]	X[15]			
HIV, HBV, HCV testing	X							
HLA Genotype and CeD Serology[3]	X							
Clinical Procedures								
Physical Exam	X[4]							X
Pregnancy Test[5]	X	X[6]	X[6]	X[6]				
Vital Signs[7]	X	X[6]			X			
Con Meds/Procedures, Incidental Gluten Exposure	X	X	X	X	X	X	X	X
3-Day GC					X[8]			
CCI [redacted]								
Safety Assessments								
Adverse Events	X	X[10]	X[10]	X[10]	X	X	X	X
Lab Tests (Safety)	X	X[6]	X[6]	X[6]	X			X
Study Drug Administration								
KAN-101/PBO Administration		X	X	X				
Additional Blood Samples								
PK Blood Sample		X[11]	X[6]	X[12]	X[15]			
ADA Sample		X[6]				X		X
CCI [redacted]								

Assessments	Screening	Treatment Period			PD Assessment		Follow-up[1]	Early Term.
Study Day	**-28**	**1**	**4**	**7**	**15**	**21**	**28 (±3)**	
CCI								

1 Phone call.

2 ECG performed pre dose (at least 5 min before infusion), 20(±5) min after start of infusion, and 1 hour (±10 min) post infusion

3 All patients will be assessed via central laboratory for HLA genotype and CeD serology (eg, tTG-IgA and DGP-IgG) at screening to confirm eligibility. For rescreening, HLA does not need to be repeated and CeD serology only needs to be repeated if >3months have elapsed from last assessment.

4 Includes weight and height at screening only.

5 Pregnancy test at screening must be serum; serum or urine tests are acceptable predose on D1, D4, and D7. Pregnancy test must be negative before each dose of study drug is administered.

6 Samples/Measurements taken pre-dose (at least 5 min prior to infusion).

7 Vital signs (pulse rate temperature, diastolic and systolic BP).

8 The GC will consist of patients self-administering 9 g of gluten protein PO for each of 3 days (D15 to D17), with the first administration in the clinic on D15. GC should be administered at approximately the same time each day.

9 CCI

10 On D1 patients will be observed in-clinic for 10 h from the start of IV infusion and followed up with by phone approximately 24 hours after dosing; on D4 and D7 (dosing days) patients will be observed for 4 h in clinic from the start of IV infusion.

11 PK samples to be taken at pre-dose (at least 5 min prior to infusion) and the following timepoints after the end of infusion: 0 (+2) min, 7 (±2) min, 15 (±2) min, 30 (±5) min, 1 h (±5 min), 2 h (±5 min), 3 h (±5 min), 4 h (±5 min) and 6 h (±5 min).

12 PK samples to be taken at pre-dose (at least 5 min prior to infusion) and the following timepoints after the end of infusion: 0 (+2) min, 7 (±2) min, 15 (±2) min, 30 (±5) min, 1 h (±5 min), 2 h (±5 min), and 4 h (±5 min).

13 CCI

14 CCI

15 Collected prior to oral gluten challenge

Abbreviations: ADA = anti-drug antibodies; BP = blood pressure; CCI; CeD = celiac disease; Con Meds = concomitant medications; Early Term = early termination; ECG = electrocardiogram; CCI; GC = gluten challenge; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; HLA = Human Leukocyte Antigen; IV = intravenous; MAD = multiple ascending dose; PBMC = peripheral blood mononuclear cell; PBO = placebo; PD = pharmacodynamics; PK = pharmacokinetics; CCI.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronym / Abbreviation	Definition
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CCI	[redacted]
CeD	celiac disease
COVID-19	Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
D	study day
DGP	deamidated gliadin peptides
DLT	dose limiting toxicity
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiogram
eCRF	electronic case report form
CCI	[redacted]
Early Term	early termination
FIH	first in human
GC	gluten challenge
GCP	Good Clinical Practice
GFD	gluten-free diet
GI	gastrointestinal
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B
HCV	hepatitis C

Acronym / Abbreviation	Definition
HIV	human immunodeficiency virus
HLA	Human Leukocyte Antigen
IBS	Irritable bowel syndrome
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
CCI	[redacted]
IgA	immunoglobulin A
IgG	immunoglobulin G
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intention-to-treat
IV	intravenous
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
LEC	Local Ethics Committee
MAD	multiple ascending dose
MBBS	Bachelor of Medicine
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NTD	non-tolerated dose
CCI	[redacted]
PBO	placebo
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetics

Acronym / Abbreviation	Definition
PLT	platelet
PO	orally
CCI	[redacted]
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMC	Study Monitoring Committee
StD	standard deviation
TEAE	treatment-emergent adverse event
tTG	tissue transglutaminase
ULN	upper limit of normal
WBC	White blood cell
WCBP	women of child-bearing potential

1. BACKGROUND

1.1. Celiac Disease

Celiac disease (CeD) is an inherited autoimmune disorder that affects the digestive process of the small intestine. When a patient with CeD consumes gluten, that individual's immune system responds by attacking the small intestine, thereby inhibiting the absorption of nutrients. CeD can present with a variety of gastrointestinal (GI) symptoms, include diarrhea, bloating, flatulence and abdominal pain, and non-GI symptoms such as anemia and vitamin deficiencies (Halfdanarson 2007, Rubio-Tapia 2013). Undiagnosed and untreated CeD has been linked to the development of other autoimmune disorders, nutritional disorders such as osteoporosis and infertility, and neurological conditions (Green 2006, Green 2001).

It has been recently estimated that 0.7% of the world-wide population has CeD, with global prevalence rates on the rise (Singh 2018). CeD is strongly associated with the Human Leukocyte Antigen *(HLA)-DQA1* and *HLA-DQB1* loci (*HLA-1*05, HAL-DQB1*02*; commonly referred to as HLA-DQ2.5) which is present in approximately 90% of CeD patients (Sollid 1989, Sollid 2012). The pathology observed in CeD patients is driven by the adaptive immune response specific to proteins generated in the digestive system after ingestion of gluten, which results in autoimmune-like pathology in the small intestine (Sollid 2013). Diagnosis is typically made by a combination of positive immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) and/or immunoglobulin G (IgG) anti-deamidated gliadin peptides (DGPs) and small intestinal biopsy demonstrating villous abnormalities while on a gluten-containing diet or following a GC (Halfdanarson 2007, Rubio-Tapia 2013).

There is currently no pharmaceutical treatment approved for the management of CeD. Patients manage their symptoms by strict adherence to a gluten-free diet (GFD), which often presents a substantial logistical and financial burden (See 2015). The effectiveness of the GFD is limited not only by motivation, access, and expense, but by uncertainty related to potential gluten content of certain medications and supplements. Adherence to the strict GFD is also limited by the ubiquity of gluten contamination in many gluten-free foods. Several studies have shown incomplete histological normalization of small bowel mucosa despite a strict GFD, with persistent villous atrophy seen in up to 79% of treated patients (See 2015). In addition to adherence challenges, some patients report persistent, life-affecting symptoms despite attempting to adhere to the GFD. Patients with CeD who adhere to a strict GFD continue to have a heavy burden of care.

Thus, there remains a strong unmet medical need for pharmacologic interventions to help alleviate the growing disease burden of CeD.

1.2. KAN-101

KAN-101 is composed of a synthetic liver-targeting glycopolymer that is conjugated to a synthetic CCI peptide domain of wheat alpha gliadin (KAN0009) recognized by the HLA-DQ2.5 haplotype. KAN0009 does not bind to the HLA DQ8 molecule. KAN-101 is a liquid formulation drug product administered parenterally via an intravenous (IV) infusion.

KAN-101 harnesses natural tolerogenic pathways in the liver (Thomson 2010) to reprogram pathogenic immune cells to become tolerant toward specific antigens. KAN-101 specifically targets the immune cells that drive CeD and leaves the otherwise healthy components of the immune system intact to perform their natural, protective functions. The mechanism by which KAN-101 induces immunologic tolerance is mediated by 3 mechanisms:

- Deletion of antigen-specific T cells
- Induction of anergy/clonal exhaustion of antigen-specific T cells
- Induction of regulatory T cells which control the antigen-specific T-cell response

In nonclinical mouse models and a non-human primate model, administration of surrogate molecules of KAN-101 were effective at inducing T-cell tolerance. From these nonclinical models, it was concluded:

- Three doses of surrogate molecules administered every 3 days was significantly more effective in inducing tolerance and improving disease outcome compared to 3 doses administered weekly.
- The doses where optimal efficacy was observed for the surrogate molecules in nonclinical models is equivalent to 1.5 to 7.0 mg/kg of KAN-101. Doses of surrogate molecules equivalent to 0.3 mg/kg of KAN-101 have demonstrated effects on disease severity in nonclinical models.
- T-cell tolerance induction can be observed as early as 1 week after drug administration in nonclinical models, supporting the observational period for the dosing of the sentinel patients across cohorts.

Previous clinical studies using an adjuvant-free mix of 3 peptides were able to induce T-cell tolerance in patients with CeD (Goel 2017). Intradermal administration of these non-targeted peptides induced moderate celiac-like GI symptoms in some patients, including nausea, abdominal pain, and vomiting, with onset within hours of drug administration. In general, these symptoms are consistent with symptoms experienced by CeD patients after ingestion of gluten (Goel 2017).

For more information on the nonclinical findings, please see the KAN-101 Investigator's Brochure.

Based on the nonclinical findings, Kanyos is initiating this first-in-human (FIH) study with KAN-101 in patients with CeD.

1.3. Selection of Patient Populations

The study population includes adults with CeD based on intestinal histology showing villous atrophy at the time of diagnosis and a record of positive serology (tTG-IgA and/or DGP-IgG). In addition, eligible patients must have HLA-DQ2.5 genotype (HLA-*DQA1*05* and HLA-*DQB1*02*) (homozygotes or heterozygotes) since the KAN0009 peptide will bind this major histocompatibility complex (MHC) molecule. Patients who are positive for HLA-DQ8 *(DQA1*03, DQB1*0302*) will be excluded, since the KAN0009 peptide will not bind to this

MHC molecule. Patients who are positive for both HLA-DQ2.5 and HLA-DQ8 will be excluded due to the presence of the HLA-DQ8 allele.

Eligible patients are required to have maintained a self-reported GFD for at least 12 months prior to study enrollment, with negative (or weak positive) TTG and DGP antibodies at screening, to ensure proper adherence and experience with GFD during the study. Patients who have a history of hyperacute or prolonged symptomology (> 48 hours) following gluten exposure will be excluded from Part B to ensure the safety of patients exposed to the GC. Patients will remain on a GFD during the study with the exception of the mandated 3-day GC in Part B.

1.4. Determination of Starting Doses and Regimen

The planned doses of KAN-101 in this FIH study allow for a robust characterization of the safety and pharmacokinetics (PK) profile of KAN-101 encompassing the physiologically active doses identified in nonclinical models. The cumulative toxicology, safety pharmacology and PK data acquired from animal studies support dosing of KAN-101 in humans. A 4-week repeat-dose Good Laboratory Practice (GLP) toxicity study examining doses up to 74 mg/kg in Sprague-Dawley rats and cynomolgus monkeys demonstrated no significant findings in either species at any dose of KAN-101 examined. The no-observed-adverse-effect-level (NOAEL) was established as 74 mg/kg (the highest dose tested) from the GLP studies in both species.

In Part A (single ascending dose [SAD]), 4 escalating dose groups are planned: 0.15 mg/kg; 0.3 mg/kg; 0.6 mg/kg; and 1.2 mg/kg. These doses are supported by the NOAEL and include doses equivalent where effects were observed in nonclinical studies. The dosing schedule requires that successively higher doses will only be administered after the safety, tolerability and available PK data of the preceding dose group have been evaluated by the Safety Monitoring Committee (SMC) and approved by the Sponsor. Doses may be adjusted based on the PK and safety findings of the preceding dose group(s).

Part B will examine multiple doses (3) of KAN-101 and includes 3 escalating dose cohorts: 0.15 mg/kg; 0.3 mg/kg; and 0.6 mg/kg. During Part B, the doses of KAN-101 will be administered every 3 days. This frequency of dosing is supported by the nonclinical experimental autoimmune encephalomyelitis (EAE) mouse model that demonstrated that dosing every 3 days was more effective than weekly dosing.

For more information on the nonclinical findings, please see the KAN-101 Investigator's Brochure.

2. OBJECTIVES

2.1. Primary (Part A and Part B)

- Assess the safety and tolerability of escalating doses of KAN-101 in patients with CeD

2.2. Secondary (Part A and Part B)

- Assess the PK of KAN-101 after single and multiple doses of KAN-101 in patients with CeD

2.3. Exploratory (Part B only)

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3. ENDPOINTS

3.1. Primary Endpoint (Part A and Part B)

- Incidence and severity of treatment-emergent adverse events (TEAEs) as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or higher

3.2. Secondary Endpoint (Part A and Part B)

- Plasma concentrations and PK parameters of KAN-101

3.3. Exploratory Endpoint (Part B only)

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4. STUDY DESIGN

Study KAN-101-01 is a Phase 1, FIH study designed to evaluate the initial safety, tolerability, and activity of KAN-101 in patients with CeD on a GFD. An overview of the 2 parts and proposed dose groups is presented in Figure 1.

4.1. PART A – Single Ascending Dose

Part A employs a SAD 3+3 design, in which patients will receive a single IV infusion of KAN-101 on Day 1 (D1) followed by 20 days of safety monitoring, which includes assessment of AEs, clinical signs and symptoms, and clinical laboratory values.

All cohorts in Part A will employ sentinel dosing, whereby the first patient in each cohort will be dosed at least 7 days prior to the subsequent patients to monitor for the acute and subacute safety of KAN-101. Based on nonclinical data, a sentinel period of 7 days should be sufficient to allow for complete drug clearance (>5 half-lives) and development of the immune tolerance mechanism.

The doses for Part A include 0.15 mg/kg (Cohort 1), 0.3 mg/kg (Cohort 2), 0.6 mg/kg (Cohort 3), and 1.2 mg/kg (Cohort 4). After the last patient within a given dose cohort has been followed for at least 7 days post-dose, a safety review will be performed by the SMC and will include review of all available safety and PK information. Dosing at the next dose level will only commence upon a recommendation from the SMC and approval by the Sponsor.

For all patients in Part A, the study will consist of a 28-day screening period, a single dose of KAN-101 administered on D1 and follow up through D21. D1 includes a 10-hour monitoring period in the clinic/hospital unit and a phone call follow up approximately 24 hours after dosing.

- If a patient is experiencing active AE(s) which require clinical monitoring at the end of the clinic/hospital unit monitoring period, the patient should not be discharged and should be followed until satisfactory resolution as determined by PI
- If feasible, patients should be advised to have someone stay with them after discharge until 24 hours have elapsed after study drug administration on D1.
- If patients do not live within 1-hour travel time of an emergency medical facility, they should remain in the clinic/hospital unit for the first 24 hours after study drug administration.
- Patients should be instructed not to drive themselves to seek emergency medical treatment.

Patients will be evaluated on D4 (±1), D8, and D21. Blood and serum samples will be collected for PK and anti-drug antibody (ADA) assessments during Part A. Patients in Part A may be replaced if they do not receive the full dose of study drug or do not complete the D8 visit, as long as the discontinuation was not due to a DLT assessed to be related to study drug. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for

safety assessments and data collection may be employed to ensure the safety of the trial participant where appropriate.

Please see Table 1 for the complete schedule of assessments for Part A.

4.2. PART B – Multiple Ascending Dose

Part B will be initiated following successful completion and SMC review of SAD Cohort 2 in Part A. This transition at Cohort 2 from single to multiple dosing of KAN-101 is supported by nonclinical models that show clearance of KAN-101 within 24 hours, and in vivo animal studies that did not show any drug accumulation when KAN-101 was given 3 times a week.

Part B employs a randomized, double-blind multiple ascending dose (MAD) design, in which 3 cohorts of patients will be assigned 3:1 to either KAN-101 or matching placebo (PBO). Patients in Part B will receive an IV infusion of KAN-101 or PBO on D1, D4, and D7. All cohorts in Part B will employ sentinel dosing, whereby the first 2 patients (1 KAN-101 and 1 PBO) in each cohort will be dosed at least 14 days prior to the subsequent patients (ie, 7 days following the third and final dose) to monitor for the acute and subacute safety of KAN-101.

The doses for Part B include 0.15 mg/kg (Cohort 5), 0.3 mg/kg (Cohort 6), and 0.6 mg/kg (Cohort 7). After the last patient dosed within a given cohort has been followed for at least 14 days, a safety review will be performed by the SMC. Initiation of the next dose cohort will commence upon recommendation by the SMC after review of available safety and PK data and approval of the Sponsor.

For all patients in Part B, the study will consist of a screening period of up to 28 days, followed by 3 doses of KAN-101, each administered on D1, D4, and D7. The first dose on D1 will be followed by a 10-hour monitoring period in the clinic/hospital unit and a phone call follow up approximately 24 hours after dosing. Subsequent doses scheduled on D4 and D7 have a 4-hour monitoring period in the clinic/hospital unit.

- If a patient is experiencing active AE(s) which require clinical monitoring at the end of the clinic/hospital unit monitoring period, the patient should not be discharged and should be followed until satisfactory resolution as determined by PI
- If feasible, patients should be advised to have someone stay with them after discharge until 24 hours have elapsed after study drug administration on D1.
- If patients do not live within 1-hour travel time of an emergency medical facility, they should remain in the clinic/hospital unit for the first 24 hours after study drug administration.
- Patients should be instructed not to drive themselves to seek emergency medical treatment.

Patients will return to the clinic on D15 to initiate oral GC and on D21 for biomarker sample collection. Blood and serum samples will be collected for PK, PD, and ADA assessments during Part B of the study. Patients in Part B may be replaced if they do not receive the full 3 doses of

study drug or do not complete the D21 visit, as long as the discontinuation was not due to a DLT assessed to be related to study drug. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the trial participant where appropriate.

To assess the PD effects of KAN-101, on D15 of Part B patients will begin a 3-day, self-administered high-dose (9 g of gluten protein) oral GC. Typically, a 3-day oral GC is not long enough to induce changes in GI histopathology, and reactions are limited to mild or moderate symptoms. Any severe symptoms experienced by patients during the GC will be treated as medically indicated. To ensure patient safety, patients with a history of hyperacute symptomology or prolonged symptoms after gluten exposure will be excluded from Part B.

The GC is positioned 1 week after the last dose to allow sufficient time for T cell tolerance induction to develop. The initial dose of the GC will be administered in the clinic, and patients will be monitored for at least 6 hours post gluten administration CCI [redacted]. GC administration on D16 and D17 will be self-administered at home, at approximately the same time as the first in-clinic administration.

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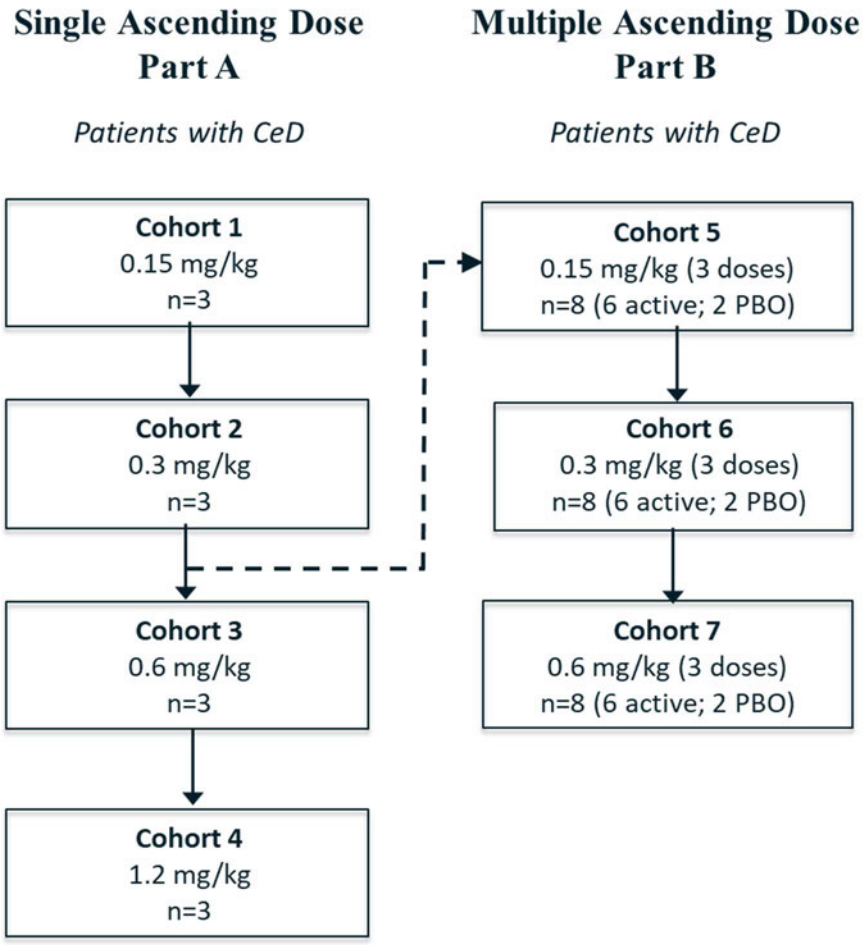
Based on data obtained during both the SAD and MAD parts of the study, the protocol may be amended to explore additional higher dose levels and dosing schedules if supported by the data, recommended by the SMC, and approved by the Sponsor.

Please see Table 2 for the complete schedule of assessments for Part B.

Figure 1: Overview Study KAN-101-01



Single Ascending Dose (SAD): 3 patients will be dosed IV with KAN-101. Initiation of the next dose cohort will commence once all patients in a cohort reach D8 postdose, and upon acceptable safety review by SMC and approval from Sponsor.

Multiple Ascending Dose (MAD): the first MAD cohort will be initiated after safety review of SAD Cohort 2. Patients randomized 3:1 to KAN-101 or PBO. Initiation of the next dose cohort will commence once all patients in a cohort reach D15 postdose, and upon acceptable safety review by SMC and approval from the Sponsor.

All cohorts will employ sentinel dosing to allow for assessment of acute and subacute reactions prior to dosing additional patients in the study.

Abbreviations: CeD = celiac disease; IV = intravenous; n = number; PBO = placebo; SMC = safety monitoring committee.

4.3. Dosing Frequency

In Part A, patients will receive a single IV infusion of KAN-101 on D1.

In Part B, patients will receive a total of 3 IV infusions of either KAN-101 or PBO (double-blind). A single IV infusion will be administered on D1, D4, and D7.

4.4. Blinding

Part A is open label.

Part B is double-blinded, such that study personnel (eg, Investigators, site coordinators) and patients are blinded to treatment assignments and will remain blinded throughout the study.

Unblinded personnel include those involved in drug preparation and allocation (eg, data systems support and pharmacists), and the study pharmacokineticist to allow for expedited review of PK data prior to SMC review.

The data for dose escalation in Part B will be presented and reviewed by the SMC in a blinded fashion.

After completion of SMC review and once all patients in the cohort have completed the study, the sponsor study team members involved in biomarker data analysis may be unblinded to complete pharmacodynamic assessments.

In the event of a medical emergency, the site may be unblinded if knowledge of the study treatment is necessary in order to provide appropriate urgent medical care.

4.5. Monitoring of Adverse Events

Patients will be monitored continuously for AEs while on study. AE severity will be assessed using the NCI CTCAE v5.0 or higher (Appendix 1).

4.6. Dose-Limiting Toxicities

Dose-limiting toxicities (DLTs) for Study KAN-101-01 include any ≥ Grade 3 AE assessed as related to KAN-101 or Grade 2 AE assessed as related to KAN-101 not resolving within 14 days; DLTs do not include those AEs attributable solely to intercurrent illness or other concomitant medications. Any DLT experienced during the study will result in study pause and review by the SMC. Any ≥ Grade 4 AE will result in notification of the FDA in parallel with the SMC and study dosing and enrollment will be paused pending review by FDA.

4.7. Dose Escalation Safety Period

In Part A, the dose escalation safety monitoring period is from the beginning of IV administration through D8. Any AEs that meet the above criteria but occur after the dose escalation safety monitoring period of Part A may be considered by the SMC in the evaluation for Part B dose selection.

The dose escalation safety monitoring period in Part B is from the beginning of the first IV administration of KAN-101/PBO through the D15 clinic visit, prior to initiating the GC.

The length of the monitoring periods for safety review is supported by nonclinical exposure data, suggesting KAN-101 will have cleared 5 half-lives, and nonclinical animal model data demonstrating that the tolerance induction mechanism can develop within 1 week of dosing. AEs and any abnormal clinical parameters, including laboratory findings, observed during this period will be used by the SMC to determine whether dose escalation should proceed.

No patient with a DLT will be replaced.

In both parts, patients will be monitored in the clinic for 10 hours following the first IV administration of KAN-101/PBO. In Part B, patients will be monitored in the clinic for 4 hours following completion of their second and third dose.

4.8. Safety Monitoring Committee

This study will utilize an SMC that will meet regularly to review all accumulated and available data, including safety and PK. The SMC will be comprised of three independent medical reviewers, including at least 1 CeD medical expert, as voting members. Non-voting members will include the study medical monitor, a medical representative from the Sponsor and other relevant study and site staff as required to address study conduct. The SMC will recommend all dose escalation decisions, and/or any recommended changes to the dosing paradigm based on review of the received data. The SMC will also make recommendations about the dose(s) selected for Part B.

4.9. Individual and Cohort Stopping Rules

During the dose escalation safety monitoring period, any DLT will result in a pause in enrollment and a thorough review by the SMC prior to treating any additional patients. Any ≥ Grade 4 AE will result in notification of the FDA in parallel with the SMC and study dosing and enrollment will be paused pending review by FDA.

For Part A, if 1 of the first 3 patients experiences a DLT in a given cohort, 3 additional patients will be enrolled and evaluated in that cohort before dose escalation can occur if recommended by the SMC and only after consultation with the FDA for any ≥ Grade 4 AE. If 2 or more patients experience a DLT at a given dose level during the dose escalation evaluation period of Part A, then that dose level will be considered a non-tolerated dose (NTD), and no further escalation will proceed.

If a patient experiences a DLT during the dose escalation safety monitoring period of Part B, no additional doses will be administered to that patient. If 1 patient experiences a DLT during the dose escalation safety monitoring period of Part B, the study will be paused to determine if any dose adjustments are needed and/or if the study should dose any additional patients. For any ≥ Grade 4 AE the study would only continue after consultation with the FDA. If 2 or more patients experience a DLT during the dose escalation safety monitoring period of Part B, then that dose level will be considered an NTD, and no further escalation will proceed.

4.10. Treatment Discontinuation

Patients will be discontinued from treatment for any of the following reasons:

- An AE that requires permanent discontinuation of study treatment*
- Noncompliance with the protocol
- Investigator decision
- Patient becomes pregnant

- Patient death
- Patient lost to follow-up
- Termination of the study by the Sponsor
- Voluntary withdrawal of consent by patient

**AEs leading to the discontinuation of KAN-101 will be followed until resolution, resolution to baseline, or until the event is considered stable or chronic.*

The reason for treatment discontinuation will be documented.

All patients will have a final Follow-Up approximately 20 days (D21±1) after the single dose of KAN-101 in Part A and approximately 20 days (D28±3) after the third and final dose in Part B, unless the patient withdraws from the study prematurely (Section 4.10).

4.11. Study Withdrawal

Patients may voluntarily withdraw from the study at any time for any reason without prejudice.

Patients will be withdrawn from the study for any of the following reasons:

- Investigator's decision
- Patient death

Patient lost to follow-up

Termination of the study by Sponsor

Voluntary withdrawal of consent by patient

5. STUDY POPULATION

5.1. Inclusion Criteria

1. Adults aged 18 to 70 years inclusive
2. Diagnosed with CeD based on positive serology (eg, tissue transglutaminase IgA antibody [tTG-IgA] and/or deamidated gliadin peptide IgG [DGP-IgG]) and intestinal histology consistent with ≥ Marsh Type II or with evidence of villous atrophy
3. Has HLA-DQ2.5 genotype (*HLA-DQA1*05* and *HLA-DQB1*02*) (homozygotes or heterozygotes)
4. Has followed a GFD for > 12 months immediately prior to study entry
5. Negative or weak positive for tTG IgA and negative or weak positive for DGP-IgA/IgG during screening
6. Male or female. Females of childbearing potential must use at least 2 acceptable birth control methods
7. Capable of understanding and complying with protocol requirements
8. Patient understands and has signed the informed consent form (ICF)

5.2. Exclusion Criteria

1. Refractory CeD
2. Selective IgA deficiency
3. Positive for HLA-DQ8 (*DQA1*03, DQB1*0302*)
4. Previous treatment with tolerance-inducing therapies for CeD
5. Known wheat allergy
6. **Part B only:** History of hyperacute (requiring medical treatment) or prolonged symptoms (> 48 hours) following gluten exposure
7. Has active inflammatory bowel disease (eg, Crohn's disease, colitis)
8. Presence of other autoimmune disorders in addition to CeD, including but not limited to type 1 diabetes, rheumatoid arthritis, psoriasis, autoimmune thyroid disease, etc.
9. Uncontrolled or significant medical conditions (including active infections or chronic hepatitis) which, in the opinion of the Investigator, preclude participation
10. Patients with clinical signs and symptoms consistent with COVID-19 (eg, fever, dry cough, dyspnea, sore throat, and fatigue) or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission

    Note: Patients who experienced symptoms consistent with COVID-19 or confirmed infection during the screening period (ie, after signing the ICF but before dosing) may be rescreened after 4 weeks

11. Patients with a prior severe course of COVID-19 requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation
12. Receipt of chronic, systemic non-biologic immunosuppressive or immunomodulatory therapies within the last 3 months (eg, methotrexate, sulfasalazine, or corticosteroids such as prednisone, etc.)
13. Positive for HIV, HBV, or HCV
14. Receipt of any vaccination within 4 weeks prior to first dose of study drug
15. Receipt of biologic immunosuppressive or immunomodulatory therapies within the last 12 months (eg, adalimumab, etanercept, certolizumab, etc.)
16. Has any of the following laboratory parameters at Screening:
    a. Hemoglobin < 10 g/dL
    b. Platelet (PLT) count < 100 x 10^9/L
    c. White blood cell count (WBC) outside the normal range and assessed as clinically significant by the Investigator
    d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) > 1.5 x the upper limit of normal (ULN)
    e. Estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2 based on the Cockcroft-Gault equation during screening
17. Average alcohol consumption of > 2 drink-equivalents per day
18. History of dermatitis herpetiformis
19. Pregnant or breastfeeding

6. STUDY PROCEDURES AND ASSESSMENTS

Time points for assessments collected throughout the study can be found in the Schedule of Assessments (Table 1 and Table 2). A brief description of each assessment can be found below.

6.1. Screening and Treatment Procedures and Assessments

6.1.1. Informed Consent

An ICF must be signed by prospective patients prior to initiating any study-specific procedures. Standard of care assessments performed prior to ICF signing may fulfill study eligibility requirements if performed within the screening period.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5) will be reviewed for each potential patient. Eligibility will be documented in the electronic case report form (eCRF).

6.1.3. Medical History, Demographics, and Celiac Disease History

Complete medical history will be obtained, including demographics, symptoms at diagnosis, disease history, and length of time on a GFD.

6.1.4. Concomitant Medications and Procedures

At screening, concomitant medications will be recorded. Assessment of any change in concomitant medications, or procedures since the last visit will occur at all further patient visits through the final Follow-Up Visit.

6.1.5. Incidental Gluten Exposure Assessment

Assessment of any incidental gluten exposure will be captured at all study visits.

6.1.6. Physical Examination and Vital Signs

A full physical examination (PE) and vital signs check will be performed at the time points specified in the Schedule of Assessments (Table 1 and Table 2). PEs will also be conducted as clinically indicated.

The PE will include an assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory, abdomen, height, and weight (baseline only). Vital signs will include temperature, pulse rate and blood pressure (BP) (sitting for 5 minutes). If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart.

Any new CS abnormality from baseline should be recorded as an AE.

6.1.7. Electrocardiogram

All electrocardiograms (ECGs) will be standard resting 12-lead ECGs performed after the patient has been supine for at least 5 minutes. Patients will be instructed to remain completely

stationary (no talking, deep breathing, sleeping or swallowing) for approximately 10 seconds during the ECG recording. When possible, serial reads on dosing days should be performed by leaving the ECG electrode pads in place for subsequent assessments to ensure comparable ECG reads. While ECGs are being acquired, patients and staff are prohibited from having devices (cell phones, fans, heaters and other radiofrequency signals) that emit electrical interference in the room. If the initial ECG at a timepoint is abnormal then the ECG should be repeated 2 additional times (approximately 2 min apart) within 15 min of the initial ECG.

When an ECG is scheduled at the same time of a blood collection, the ECG will be obtained prior to the blood collection. ECG occurring near meals will take place prior to meals.

All study ECGs will be evaluated by the site Investigator or qualified designee ("local reader") and interpreted for safety. The local reader will provide global interpretation of normal, abnormal and not clinically significant, abnormal and clinically significant, or unable to evaluate. Additionally, ECGs will be transmitted electronically to a central ECG core lab for cardiologist over read.

ECGs will be conducted as outlined in Table 1 and Table 2. The local reader will review the screening ECG to confirm eligibility. For rescreening, the ECG only needs to be repeated if >3 months have elapsed from last assessment.

6.1.8. Clinical Laboratory Tests

The following laboratory parameters will be measured at screening and at the time points specified in the Schedule of Assessments (Table 1 and Table 2) and will be analyzed locally or centrally by a certified laboratory:

- A serum pregnancy test during screening for all women of child-bearing potential (WCBP)
- Serum or urine pregnancy testing for all WCBP prior to each dose
- Hematology laboratory parameters include WBC count, hemoglobin, hematocrit, PLT count, and WBC differential
- Blood chemistry laboratory parameters, including blood urea nitrogen, creatinine, glucose, AST, ALT, ALP, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), amylase, lipase, albumin, magnesium, calcium, and phosphorus
- Coagulation laboratory parameters, including prothrombin time, partial thromboplastin time or activated partial thromboplastin time, and international normalized ratio
- Complete urinalysis with qualitative analysis for protein (dipstick)
- Human immunodeficiency virus (HIV), hepatitis B (HBV) (HBsAg, anti-HBc and anti-HBs), and hepatitis C (HCV) testing (screening only)

The following laboratory tests will be performed centrally at screening as specified in the Schedule of Assessments (Table 1 and Table 2):

- HLA DQ2.5 and HLA DQ8 testing
- Transglutaminase (tTG) and deaminated gluten peptides (DGP) IgA/IgG

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

For re-screening, the HLA does not need to be repeated and the tTG and DGP antibody tests should only be repeated if >3months have elapsed from end assessment.

Unscheduled assessments should be performed as clinically indicated.

For any out-of-range laboratory findings during screening, repeat laboratory testing may be performed at the discretion of the Investigator. Abnormal laboratory findings at screening should be recorded as medical history only if considered CS.

Clinical laboratory assessments should be performed prior to KAN-101/PBO infusion when applicable.

Laboratory findings assessed by the Investigator as CS, including but not limited to, those findings resulting in a drug interruption/hold/reduction/discontinuation or medical intervention, should be repeated to verify the out-of-range findings, followed to a satisfactory clinical resolution, and reported as an AE(s) (see Section 11.1.1 for definition of an AE).

6.1.9. KAN-101 Administration

Detailed instructions on the administration of KAN-101 can be found in Section 10 .

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6.1.11. Gluten Challenge

All patients enrolled in Part B of the study will undergo a GC for 3 days, from D15 to D17. During these 3 days, patients will self-administer 9 g of gluten protein orally (PO) once each day at approximately the same time every morning. The first dose of gluten will be administered in the clinic, and the patient will be observed for at least 6 hours to monitor for hyperacute reactions requiring medical treatment and collection of biomarker samples. Patient compliance will be recorded by the study Investigator.

6.1.12. Pharmacokinetic Sampling

PK sample collection time points are shown in Table 1 and Table 2.

The exact date and time of each sample collection must be recorded for all collected samples.

Refer to the KAN-101-01 Laboratory Manual for details on processing, storage, and shipment of PK samples.

6.1.14. Adverse Events

All AEs should be captured on the eCRF from the time of signing of ICF through the final Follow-Up Visit/phone call. AEs considered at least possibly related to KAN-101 should be followed until resolution, return to baseline, or deemed chronic or stable.

All serious adverse events (SAEs) will be immediately reported to the Sponsor from the time of signing the ICF through the Follow-Up Visit/phone call or until the patient has been deemed to be a screen failure. After completion of the AE reporting period (ie, through the final Follow-Up Visit/phone call), only SAEs attributed to KAN-101 must be reported to the Sponsor.

See Section 11.2 for a full description of the collection and reporting of AEs during this study.

6.2. Safety Follow-up Visit

All patients in Part A will have a final Follow-Up at D21 (±1), 20 days after the single administration of KAN-101.

All patients in Part B will have a final Follow-Up phone call at D28 (±3), approximately 20 days after the final administration of KAN-101 on D7.

Ongoing AEs considered at least possibly related to KAN-101 treatment should be followed until resolution, return to baseline, or are considered stable or chronic.

7. CONCOMITANT MEDICATIONS

7.1. Prohibited Concomitant Therapies

During the study period, any additional therapies to treat CeD or other investigational agents are prohibited, including biologic or non-biologic immunosuppressive or immunomodulatory therapies. In addition, non-investigational immunosuppressive and immunomodulatory therapies are prohibited (eg, systemic corticosteroids). Patients should avoid the use of probiotic supplements during the study period. All vaccines are prohibited for at least 4 weeks prior to dosing and during the study period.

7.2. Permitted Concomitant Therapies

All patients are required to maintain a GFD during the study. Any other medication that is considered necessary for the patient's welfare that is not expected to interfere with the evaluation of KAN-101 may be given at the discretion of the Investigator. In cases involving concomitant therapies whose predicted interference with KAN-101 is unknown to the Investigator, the Sponsor should be contacted for discussion. Patients being treated for IBS symptomology will be allowed to continue therapy (eg, dicyclomine) unless the drug is specifically prohibited (Section 7.1).

Antidiarrheal (eg loperamide) or antiemetics (eg metoclopramide) may be used during the GC if warranted by symptomology unless the drug is specifically prohibited (Section 7.1).

Any medication (including over the counter or prescription medications, vitamins, and/or herbal supplements) that the patient receives after enrollment through the last study visit must be recorded on the eCRF.

8. CONTRACEPTION AND PREGNANCY

The effects of KAN-101 on conception, pregnancy, and lactation are unknown.

At screening, all women who are not surgically sterile or postmenopausal must agree to use at least 2 medically acceptable methods of birth control (defined as the use of an intrauterine device, a barrier method with spermicide, condoms, any form of hormonal contraceptives, or partner sterility) for the duration of the study. WCBP who practice complete sexual abstinence are NOT required to commit to use of 2 methods of birth control. Complete sexual abstinence is only acceptable when it is the usual/preferred lifestyle of the subject and has been so for at least 3 months prior to Screening. Periodic abstinence, calendar timing methods of contraception, or withdrawal are NOT acceptable methods of contraception.

At screening, all men who are not sterile (biologically or surgically) must commit to the use of 1 reliable method of birth control (e.g. condoms with spermicide, sterile partner) for the duration of the study.

A serum pregnancy test will be administered during screening for all WCBP. A serum or urine pregnancy test will be administered to all WCBP prior to each dose of study drug and must be confirmed negative before administration of study drug.

9. OTHER RESTRICTIONS RELATED TO COVID-19

Patients will be advised to adhere to local requirements for reduction of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure while ambulatory. All patients should be called 1 day prior to every visit for assessing COVID-19 signs and symptoms and asked not to attend the site if infection is suspected. In addition, patients will be asked whether they have had any contact with a person who has a confirmed infection. If applicable, patients will be referred to the local health care system. Physical distancing and person-to-person contact restrictions should be applied and explained to patients while staying at the study site, if required by local requirements. Where physical distancing is not possible, study participants will be asked to use face masks and/or gloves, if deemed appropriate by the Investigator and site staff and guided by local requirements.

10. KAN-101 MATERIALS AND MANAGEMENT

10.1. KAN-101 and Placebo

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10.2. Dosage and Administration

KAN-101 is provided as a frozen concentrated solution CCI [redacted] which will be diluted into 250 mL normal saline.

Administration will be by IV infusion over approximately 30 minutes.

For Part A, patients will receive a single IV infusion of KAN-101 only (no PBO).

For Part B, patients will receive 3 IV infusions, each spaced 3 days apart, of a given dose of either KAN-101 or PBO. All doses will be prepared as outlined in the KAN-101-01 Pharmacy Manual by an unblinded pharmacist.

Study treatment (KAN-101 or PBO) should be administered over 30 minutes under the supervision of a physician or other medically qualified study personnel experienced in the use of IV agents and in a facility equipped to manage medical emergencies. In the event of a Grade 3 infusion-related reaction (IRR), the total infusion duration may be increased to 1 hour (please see Section 10.5 for more information). In cases where a temporary interruption is required, the total infusion should be completed within 24 hours of thawing the drug product. See Section 10.5 for detailed guidance regarding infusion administration interruptions due to infusion reactions.

Please refer to the KAN-101 Pharmacy Manual for detailed administration instructions.

10.3. Storage

KAN-101 is supplied in vials for single use. KAN-101 is to be stored at -20°C and protected from light in a temperature-monitored, locked freezer. Additional details on storage conditions are available in the KAN-101 Pharmacy Manual.

10.4. Post-Infusion Medications

No specific post-infusion medications are required for KAN-101, but may be administered at the discretion of the Investigator.

10.5. Infusion-Related Reactions

If an IRR occurs during KAN-101 administration, the following treatment recommendations are provided and may be modified per local treatment standards and guidelines as appropriate.

- Grade 1 (mild): Infusion rate modification not indicated. Administer symptomatic treatment (eg, antihistamines, antipyretics, antiemetics) as needed. Closely monitor patient until resolution. Prophylaxis with diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg is recommended at least 30 min prior to future KAN-101 infusions
- Grade 2 (moderate): Slow infusion to ≤ 50% of the original infusion rate and treat symptoms with appropriate medical therapy, including but not limited to antihistamines, antipyretics, and analgesics. Increase monitoring of vital signs as medically indicated until patient is deemed stable. Prophylaxis with diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg is recommended at least 30 min prior to future KAN-101 infusions
- Grade 3 (severe): Stop infusion and institute appropriate symptom-directed therapy, including but not limited to antihistamines, antipyretics, corticosteroids, bronchodilators, and O_2. Increase monitoring of vital signs as medically indicated until patient is deemed stable. If the reaction has not resolved within 6 hours, the remainder of the infusion will not be administered and KAN-101 will be permanently discontinued. Following the completion or termination of a restarted infusion due to an IRR, all patients must be monitored until resolution of symptoms or for 2 hours in the absence of additional symptoms. Prophylaxis with diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg is required at least 30 min prior to future KAN-101 infusions. The next infusion should initiate at a rate of 2 hours per dose, or 50% of the rate at which the reaction occurred. If no IRRs are observed within the first 30 minutes, the infusion rate may increase to the 1-hour-per-dose rate as outlined in Section 10.2. Permanently discontinue KAN-101 upon a second occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Stop infusion and immediately institute appropriate symptom directed therapy and supportive measures as necessary, including, but not limited to, corticosteroids, bronchodilators, O_2/respiratory support, and vasopressors. Hospitalization and/or intensive care unit admission may be indicated. Permanently discontinue treatment.

10.6. Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of KAN-101 received and comparing it with the accompanying drug order form. All unused KAN-101 will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of any KAN-101 at the clinical study site per site procedures, or if necessary, all KAN-101 will be returned to the Sponsor or its designee. Disposition of all KAN-101 should be documented, including any KAN-101 that is lost or damaged.

10.7. Assignment to Treatment

Once a patient has met all entry criteria, the Interactive Response Technology (IRT) will be used to generate a distinct patient identifier. If a patient discontinues from the study, the patient identifier will not be reused and the patient will not be allowed to re-enter the study.

In Part A, patients will be assigned to receive open-label KAN-101 at a dose level based on the next available spot in the cohort(s) currently being enrolled.

In Part B, the first 2 eligible patients within each cohort will be randomized via IRT in a 1:1 ratio to receive either KAN-101 or PBO. After completion of the sentinel dosing, the remaining 6 patients in each cohort will be randomized 5:1 to receive KAN-101 or PBO.

11. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1. Adverse Events

11.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with study participation, whether or not consider related to study treatment.

An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include worsening of a pre-existing medical condition as well as CS changes from baseline laboratory values/conditions. Worsening of the preexisting medical condition (eg, diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study is not considered an AE.

11.1.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (documented as medical history on the eCRF) is not considered an SAE
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is considered an important medical event
  - If an AE does not meet 1 of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of an ‘Important Medical Event’. Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

11.2. Procedures for Recording and Reporting Adverse Events

11.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs and SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through the Final Study Visit/phone call. An AE will be followed until it is resolved, has returned to baseline, or is determined to be a stable or chronic condition.

At each protocol-required visit (including safety follow-up phone call) during the study, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or nonserious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained
- Dates of onset and resolution
- Severity as defined per protocol
- Assessment of relatedness to KAN-101/PBO
- Action taken with each KAN-101/PBO dose as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (eg, for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (eg, for sepsis secondary to pneumonia, both events should be recorded).

Confirmed and suspected SARS-CoV-2 infections and/or COVID-19 cases will be recorded in the AE eCRF.

11.2.2. Relationship to KAN-101

The Investigator must assess whether the AE may be related to KAN-101 (study drug) or any protocol mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is “Not Drug Related”:

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study patient’s medical record).
- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is “Drug Related”:

- Possible: There is an association between the event and the administration of KAN-101, and there is a plausible mechanism for the event to be related to the study

product; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.

- Probable: There is an association between the event and the administration of KAN-101, there is a plausible mechanism for the event to be related to KAN-101, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of KAN-101, there is a plausible mechanism for the event to be related to the KAN-101 and causes other than KAN-101 have been ruled out and/or the event re-appeared on re-exposure to KAN-101.

11.2.3. Adverse Event Severity

The Investigator will assess the Grade of the AE per the NCI-CTCAE v5.0 or higher (Appendix 1). Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- 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 self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 11.1.2.

11.2.4. Abnormal Laboratory Values

The Investigator is responsible for reviewing clinical laboratory tests determining whether an abnormal value represents a CS change from the patient's baseline value. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should **not** be recorded as AEs. In general, an abnormal laboratory test result should be reported as an AE if the laboratory result:

- Requires an adjustment or discontinuation of KAN-101
- Requires treatment with or adjustment to concomitant medications
- Is considered to be an AE by the Investigator

11.2.5. Medication Errors, Misuse, and Abuse of KAN-101

Overdose, medication error, misuse, and abuse are defined as follows:

- Overdose: refers to the administration of a quantity of KAN-101 given per administration or cumulative, which is above the maximum dose according to the protocol
- Medication error: refers to an unintentional error in dispensing or administration of KAN-101 not in accordance with the protocol

Off-label use: relates to situations where KAN-101 is intentionally used for medical purpose not in accordance with the protocol

- Misuse: refers to situations where KAN-101 is intentionally and inappropriately not used in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of KAN-101, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to KAN-101 because of one's professional or non-professional occupation

Overdoses, medication errors, abuse, or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

11.2.6. Reporting of Serious Adverse Events

SAEs will be recorded on the appropriate eCRF and reported to the Sponsor within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to KAN-101, from the time of signing ICF through the final Follow-Up Visit/phone call.

The initial SAE CRF must be as complete as possible and include details of the current illness and SAE as well as an assessment of the relationship between the event and KAN-101. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor or designee, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE considered related to KAN-101, occurring more than 30 days after the last dose of KAN-101, the SAE must be reported as described above.

11.2.7. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committee, and Institutional Review Board

The Sponsor or designee will determine expectedness of the Sponsor's product for each reported SAE based on the appropriate reference safety information per local country requirements. The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Investigator will notify the appropriate Institutional Review Board (IRB)/Local Ethics Committees (LECs) of serious, related, and unexpected AE(s), or significant risks to patients, per

local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor or IRBs/LECs.

11.2.8. Pregnancy and In Utero Drug Exposure

KAN-101 has not been evaluated in pregnant or nursing women. Thus, pregnant women or WCBP who are not using effective contraception are excluded from this study (see Section 8 and Section 6.1.8 for instructions on birth control and pregnancy testing, respectively).

Pregnancies occurring in patients, or partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment through the Safety Follow-Up Visit after the patient's last dose of KAN-101. If a pregnancy occurs in a patient, KAN-101 must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy by recording it on the appropriate CRF.

The Investigator will follow the pregnant patient until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the outcome. The Investigator will provide this information by recording it on the appropriate CRF. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant patient experiences an SAE during pregnancy, or the outcome of the pregnancy meets any of the serious criteria (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (ie, report the event to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor or designee. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in-utero exposure to KAN-101 should also be reported to the Sponsor or designee.

12. STATISTICAL METHODS

Details of the statistical methods for this study will be documented in a Statistical Analysis Plan (SAP). When there is a difference between the final approved SAP and the protocol, the methods described in the final SAP will prevail.

Statistical methods will be primarily descriptive in nature. No hypothesis will be formally tested. For Part A, the data will be listed by dose group. For Part B, summary statistics will be provided by dose group. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (n), mean, standard deviation (StD), median, and range (minimum and maximum).

Part A and Part B PK will be analyzed separately and together where appropriate.

12.1. Sample Size

In Part A, the number of patients enrolled into a cohort will be based on safety and tolerability, and will employ a traditional 3+3 design. Under this model, Part A may enroll between 12 and 24 patients across 4 dose cohorts, depending upon what toxicities are observed. No formal hypothesis testing is planned for Part A. The PK data obtained in Part A will be combined with the PK data obtained following first dose of KAN-101 in Part B.

In Part B, the total sample size of 24 patients (n=18 KAN-101; n=6 PBO) across 3 dose cohorts was chosen to allow for a comparison of safety, PK, and PD between KAN-101 and PBO. A sample size of 6 active patients per cohort in Part B allows for an 0.80 power to detect a treatment-related AE occurring at an event rate of 0.25.

12.2. Analysis Sets

The main analysis sets are defined in this section. Additional analysis sets may be defined in the SAP.

- **The All-Treated Analysis Set** is defined as all patients who received any amount of study drug with treatment group based on the dose level received. This analysis set will be the primary analysis set for all safety endpoints.
- **The PK Analysis Set** will include all enrolled patients who received at least one dose of KAN-101 and have at least one measurement. This analysis set will be used for the analysis of PK parameters as further defined in the protocol.
- CCI [redacted]

12.3. Background Characteristics

12.3.1. Patient Disposition

The number and percentage of patients in each disposition category (eg, enrolled, included in each Analysis Set, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by dose level and cohort.

For each part of the study, the All-Treated Analysis Set will be used as the basis for percentages, as appropriate.

12.3.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by treatment group and cohort for the All-Treated Analysis Set: sex, race, age, years since CeD diagnosis, and years on GFD. Additional parameters may be provided in the SAP.

12.4. KAN-101 Exposure

The summary statistics of exposure will be tabulated by study part and by dose group. In the summary, the following will be included:

- the cumulative number of days of exposure
- the number of IV infusions completed
- the relative dose intensity

All variables are predefined:

- The relative dose intensity is defined as the percentage of the planned treatments completed. It is the ratio of the cumulative actual dose (mg) and cumulative planned dose (mg) times 100. In this definition,
- the cumulative actual dose (mg) is the sum of the actual doses (mg) that the patient receives during the study
- the cumulative planned dose (mg) is the cumulative number of days of exposure times the planned dose level (mg)

All analyses within this section will be based on the All-Treated Set unless otherwise specified.

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12.6. Safety Analyses

The Dose-Escalation Safety Analysis Set will be used to evaluate safety within the dose-escalation phase of Part A and Part B. The number and type of AEs experienced by patients will be summarized for each dose level, accompanied by a by-patient listing of potentially dose-limiting AEs events. This analysis will include all DLTs between D1 to D8 for Part A and all DLTs between D1 to D15 for Part B, which are the time periods that constitute the safety monitoring period for dose-escalation.

All-Treated Analysis Set will be used to evaluate all other safety endpoints. The number and type of AEs experienced by patients will be summarized for each dose level, accompanied by a by-patient listing of all AEs. The listing will include the description, severity, and relationship of the events to KAN-101.

For Part A and Part B, safety data, including vital signs, ECGs, laboratory test results, PEs, and AEs will be summarized by dose and assessment time points, as appropriate.

12.7. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v22.0 (MedDRA March 2019) or higher and will be graded according to the NCI-CTCAE v5.0 or higher (Appendix 1).

Summaries of AEs will include TEAEs. A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to the final Follow-Up Visit/phone call after the last dose of KAN-101 or PBO.

For Part A and Part B, AEs will be summarized overall and by dose group.

TEAEs will be summarized by the frequency within MedDRA system organ class and preferred term. Separate tabulations will also be provided for TEAEs related to study drug, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥ Grade 3 in severity. Treatment-emergent SAEs and SAEs related to study drug will also be tabulated.

Detailed information of AEs will be included in a listing.

12.8. Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System units. All statistical analyses will be by dose group.

Summary statistics for laboratory values including change from baseline will be tabulated for scheduled visits. Shifts in Grade from baseline to the maximum post-baseline (including unscheduled) grade will be summarized by number and percentage of patients within each category. Abnormality of laboratory data will be listed for patients with ≥ Grade 3 in severity.

A listing of individual patient hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled timepoints.

12.9. Pharmacokinetic Analyses

Blood samples will be collected for measurement of KAN-101, as specified in Table 1 and Table 2. The timing of sampling may be altered based on the emerging PK data. The adjustment of the PK sampling schedule is not considered to be a substantial amendment so long as the total number of plasma PK samples and the total blood volume to be collected from each participant will not change. Any adjusted sampling time points will be documented appropriately.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time of PK blood sampling will be recorded by the Investigator or designee in the CRF, as appropriate.

For the final analysis, PK parameters of KAN-101 will be determined from the plasma concentration-time data. Parameters will be calculated by noncompartmental modeling methods, using Phoenix WinNonlin 8.0 or higher, using actual sampling times where relevant. The parameters that will be calculated are defined in Table 3, and will be calculated for single or multiple dosing of KAN-101, as appropriate. Not all listed parameters may be calculable, and additional parameters may be calculated, if needed, to fully characterize the available data.

Table 3: Pharmacokinetic Parameter Definitions

Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time to first occurrence of maximum observed plasma concentration
C_{trough}	Pre-dose plasma concentration
AUC_{72}	Area under the plasma concentration-time curve from time 0 to 72 hours post-dose
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the last measurable time point
AUC_{inf}	Area under the plasma concentration-time curve extrapolated to infinity
AUC_{tau}	Area under the plasma concentration-time curve over the dosing interval
$t_{1/2}$	Terminal elimination half-life
CL/F	Apparent oral clearance
V_z/F	Apparent volume of distribution after a single dose
$R_{acc,AUC}$	Accumulation ratio based on AUC
$R_{acc,Cmax}$	Accumulation ratio based on C_{max}

Statistical evaluations of PK data will include dose proportionality assessment using C_{max}, AUC_{last}, and AUC_{inf}.

For cohort by cohort PK analysis, not all PK parameters may be calculated, and noncompartmental analysis done may be done using nominal times.

Additional details on the PK analyses will be provided in a PK analysis plan.

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13. STUDY ADMINISTRATION

13.1. Good Clinical Practice Statement

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

13.2. Informed Consent

The Sponsor or designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/ Independent Ethics Committee (IEC) requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient prior to enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a patient will be asked if he/she is willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local country requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol which necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

13.3. Patient Confidentiality

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by patient number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include patient medical history.

The Investigator must ensure that patient anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by

their assigned patient number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

13.4. Institutional Review Board/Ethics Committee Requirements

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical study site. The Principle Investigator (PI) must submit written approval from the IRB to the Sponsor before he or she can enroll any patient into the study.

The PI is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/IEC annually or as required by the IRB, regulations, and guidelines.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

13.5. Case Report Forms and Source Documentation

eCRFs will be provided for the recording of all data. The PI/Sub-Investigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

13.6. Study Monitoring

Before the first patient signs the ICF to participate in the study, the Sponsor or designee will visit the study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities related to the protocol and the responsibilities of the Sponsor or designee
- Confirm that the Investigator(s) (and other personnel involved with the study) have not invoked sanctions or demonstrated any scientific misconduct or fraud

During the conduct of the study, the Sponsor or designee will maintain regular contact and visits to the clinical study site to:

- Provide information and support the Investigator
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

13.7. Quality Assurance

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, and regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents, including source documents, and must agree to allocate his/her time and the time of the study staff to the auditors in order to discuss findings and issues.

Monitoring visits at site will be limited to a minimum required as deemed appropriate during the COVID-19 pandemic.

13.8. Study or Clinical Site Termination

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- Decision on the part of the Sponsor to suspend or discontinue testing the study treatment

Conditions that may warrant termination of a study site include, but are not limited to:

- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical study site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, the Sponsor and the Investigator(s) will assure that adequate consideration is given to the protection of the patients' interests.

13.9. Duration of the Study, Expected Duration of Patient Participation, and End of Study

The study is planned to initiate enrollment in January 2020 with the last study visit in June 2021.

In Part A of the study, enrolled patients will receive a single IV infusion of KAN-101 on D1 and will be monitored through D21. Thus, the total length of patient participation, which includes screening, is approximately 49 days.

In Part B of the study, enrolled patients will receive 3 IV infusions of KAN-101, each on D1, D4, and D7, with a final follow-up phone call on D28. Thus the total length of patient participation, which includes screening, is approximately 56 days.

13.10. Records Retention

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, eCRFs, KAN-101 inventory, IRB, and Sponsor or

designee correspondence pertaining to this study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for KAN-101, or for 2 years after the last shipment and delivery of KAN-101 for investigational use on study, or as long as required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing or relocating study records for any reason.

13.11. Publications

Publication by the clinical study site(s) of any data from this study must be carried out in accordance with the Clinical Trial Agreement.

14. REFERENCES

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[redacted]

APPENDIX 1. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

CTCAE Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA Lowest Level Term.

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through Grade 5 with unique clinical descriptions of severity for each AE based on this 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 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

A Semi-colon indicates ‘or’ within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Protocol Amendment 1, Version 2 (27 January 2020)

• Updated language regarding pausing and stopping criteria to include reporting any ≥ Grade 4 AE to FDA prior to dosing any additional subjects. This has been modified to reflect FDA feedback.

• Updated language defining the Safety Monitoring Committee to reflect FDA feedback on the independence of the SMC review

9.8.1.2 Protocol Amendment 2, Version 3 (4 March 2020)

• Clarified and expanded observations from nonclinical models

• Updated Language to clarify and expand acceptable forms of birth control for WCBP

• Modified Dose Levels

o A subject received a single dose of 1.5 mg/kg KAN-101 and experienced symptoms consistent with the ingestion of gluten. Due to these events, Anokion decided to lower the doses explored in the KAN-101-01 study.

o The doses for Part A:

- Original planned doses: 1.5 mg/kg (Cohort 1), 3.75 mg/kg (Cohort 2), 7.5 mg/kg (Cohort 3), and 15 mg/kg (Cohort 4)
- New planned doses: 0.15 mg/kg (Cohort 1), 0.3 mg/kg (Cohort 2), 0.6 mg/kg (Cohort 3), and 1.2 mg/kg (Cohort 4)

o Doses for Part B:

- Original planned doses: 1.5 mg/kg (Cohort 5), 3.75 mg/kg (Cohort 6), and 7.5 mg/kg (Cohort 7)
- New planned doses: 0.15 mg/kg (Cohort 5), 0.3 mg/kg (Cohort 6), and 0.6 mg/kg (Cohort 7)

• Updated Starting Dose and Dose escalation section of the synopsis to reflect new starting dose and included explanation for reduction

Protocol Amendment 3, Version 4 (28 April 2020)

CCI [redacted]

Protocol Amendment 4, Version 5 (14 September 2020)

• COVID updates/modifications added

• Window for SAD study visit D4 provided (±1 day)

• Removal of PK sample on SAD D4 – due to short plasma half-life of KAN-101 (less than 20 minutes) the drug will clear 5 half-lives within the 6 hours of sampling on D1, therefore the D4 sample is not required to establish the clearance of KAN-101

- CCI [redacted]

Protocol Amendment 5, Version 6 (6 January 2021)

- Upon consultation with the FDA, the length of time for in-clinic/hospital unit observation on D1 has been reduced from 24 hours to 10 hours to reduce patients COVID-19 exposure risk.
- Language has been added to allow for replacement of patients who do not receive full dose(s) of study drug as long as they do not discontinue due to a DLT assessed as related to study drug
- Statistical language has been updated to align with SAP
- Inclusion criteria #5 has been updated to allow enrollment patients with negative or weak positive tTG-IgA (defined as > 2 x ULN)
- Exclusion Criteria #12 has been modified to clarify that systemic non-biologic immunosuppressive or immunomodulatory therapies within the last 3 months should be exclusionary
- Clarified that for rescreening that:
    - HLA testing does not need repeating
    - CeD serology only needs to be repeated if > 3 months have elapsed from last assessment
    - CCI [redacted]
    - ECG only needs to be repeated if > 3 months have elapsed from last assessment
- CCI [redacted]
- Clarified blinding language to include that after completion of SMC review and once all patients in the cohort have completed the study, the Sponsor study team may be unblinded to perform biomarker analysis

Protocol Amendment 6, Version 7 (29 March 2021)

- To enhance patient safety in KAN-101-01 study, safety ECG assessments added on certain dosing days pre-dose, during infusion and post-dose