Title Page

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

Study Intervention Number:	KAN-101
Study Intervention Name:	N/A
US IND Number:	19492
EudraCT/EU CT Number:	N/A
ClinicalTrials.gov ID:	NCT05574010
Pediatric Investigational Plan Number:	N/A
Protocol Number:	KAN-101-02
Phase:	Phase 1b/2

Brief Title:

A Study of Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of KAN-101 in People With Celiac Disease

Document History

Document	Version Date
Amendment 3	30 Jan 2024
Amendment 2	06 Nov 2023
Amendment 1	21 Jun 2023
Original protocol	31 Aug 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 3 (30 January 2024)

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Modified Part B design as follows: (a) Updated number of participants enrolled in Part B to "approximately 16 participants (4 participants per treatment group)" (b) Updated primary and secondary endpoint analysis and estimands by removing power calculations and adding "descriptive summaries will be reported" in relevant sections	After review of emerging safety data, the study design is modified to close Part B after 16 participants enrolled. These changes were implemented to ensure greater participant safety, with the assumption that screening GC prior to dosing was leading to sensitization and thereby, higher number and severity of TEAEs observed in Part B compared to Part A, where participants were dosed without prior GC. Accordingly, primary endpoint analysis and estimands were updated.	All Sections Section 1 Protocol Summary Section 3 Objectives, Endpoints and Estimands Section 4 Study Design Section 5 Study Population Section 6 Study Intervention(s) and Concomitant Therapy Section 8 Study Assessments and Procedures Section 9 Statistical Considerations

Description of Change	Brief Rationale	Section # and Name
Added Part C to study design including relevant subsections	In Part C, screening GC is not present and additional assessments are added.	All Sections Section 1 Protocol Summary Section 3 Objectives, Endpoints and Estimands Section 4 Study Design Section 5 Study Population Section 6 Study Intervention(s) and Concomitant Therapy Section 8 Study Assessments and Procedures Section 9 Statistical Considerations
Added clarification that efficacy assessments are not performed, instead PD activity is being measured	The primary objective of the study is to evaluate PD activity.	Section 8.2 Efficacy Assessments Section 8.4.8.1 Lack of Efficacy
Non-substantial modifications		
Added "and Part C" (in addition to Part B) to the title, subtitle, text, and notes wherever applicable	When Part C activities are similar to Part B and no additional description is needed, the sections are modified with adding "Part C" to relevant sections.	All Sections Section 1 Protocol Summary Section 2 Introduction Section 3 Objectives, Endpoints and Estimands Section 4 Study Design Section 6 Study Intervention Section 8 Study Assessments and Procedures Section 9 Statistical Considerations Section 10 Supporting Documentation and Operational Considerations
Updated language to clarify screen failure	Updated for clarity.	Section 5.4 Screen Failures

Description of Change	Brief Rationale	Section # and Name
Added blood volumes for Part C	In Part C, volume of blood collected is different than Part B.	Section 8.1 Administrative Procedures
Updated blood volumes for Parts A and B	Updated blood volumes according to the actual blood volume collected in Parts A and B.	Section 8.1 Administrative Procedures
Added "when collected, ECG values should be entered in clinical database" for ECG assessment	Updated for clarity.	Section 8.3.3 Electrocardiograms
Added hsCRP to clinical laboratory tests table	Added for a more comprehensive chemistry panel in Part C.	Section 10.2 Clinical Laboratory Tests
Moved the summary of changes for previous amendments to Appendix 12	Moved to align with the updates in protocol template.	Section 10.12 Appendix 12: Protocol Amendment History
Added updated language for emergency contact information	The process for contacting a medically qualified individual has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a study team contact list, thereby, replacing emergency contact card with study information card.	Section 10.1.11 Sponsor's Medically Qualified Individual Section 10.1.13 Appendix 13: Abbreviations
Other editorial changes made for consistency and alignment	Editorial	Throughout the document

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1b Open-Label/ Phase 2 Double-Blind Placebo-Controlled Study for Pharmacodynamic Activity, Pharmacokinetics, Safety and Tolerability of KAN-101 in Patients With Celiac Disease

Brief Title:

A Study of Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of KAN-101 in People With Celiac Disease

Regulatory Agency Identification Number(s):

US IND Number:	19492
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT05574010
Pediatric Investigational Plan Number:	N/A
Protocol Number:	KAN-101-02
Phase:	Phase 1b/2

Rationale:

The purpose of the study is to evaluate the safety, tolerability, PK parameters, and plasma biomarker (IL-2) response of participants with CeD treated with KAN-101.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Part A: • Assess the safety and tolerability of KAN-101 in participants with CeD.	**Part A:** • Incidence and severity of TEAEs as assessed by CTCAE.	**Part A:** • Not applicable.
Part B: • Examine the biomarker response (IL-2) in peripheral blood following GC and after dosing.	**Part B:** • Change in magnitude of IL-2 response pre-and post-GC in peripheral blood from baseline screening to Day 15.	**Part B:** **Estimand 1:** This estimand is a treatment policy, observed data will be used for summary without regard to intercurrent events. It includes the following 5 attributes: Population: Participant with celiac disease as defined by the Part B inclusion and exclusion criteria.

Objectives	Endpoints	Estimands
		Variable: Change in magnitude of IL-2 response pre- and post-GC from baseline to Day 15. Treatment conditions: 3 dose groups of KAN-101 or PBO. Intercurrent Events: Intercurrent events will not be considered for analysis. Population level summary: Mean, geometric mean ratio of post-GC vs pre-GC in IL-2 at Day -21 and Day 15 by treatment.
Part C: • Compare change in biomarker (IL-2) response following GC in participants with CeD treated with KAN-101 versus PBO.	**Part C:** • Change in levels of IL-2 from pre-GC to post-GC on Day 15.	**Part C:** **Estimand 2:** The primary estimand is the hypothetical estimand, which estimates the treatment effect of KAN-101 vs PBO for IL-2 under the scenario of no intercurrent events. It includes the following 5 attributes: Population: Participant with celiac disease as defined by the Part C inclusion and exclusion criteria. Variable: log transformed IL-2 change from pre-GC to post-GC on Day 15. Treatment conditions: 3 dose groups of KAN-101 or PBO. Intercurrent Events: Prohibited medication, incomplete GC on Day 15, and discontinuation of study intervention. All data collected after any intercurrent events will be excluded. Population level summary: The LSM difference of the change from pre-GC to post-GC (log transformed) between each KAN-101 group and PBO.
Secondary:	**Secondary:**	**Secondary:**
Part A, Part B and Part C: • Assess the PK of multiple doses of KAN-101 in participants with CeD.	**Part A, Part B and Part C:** • KAN-101 plasma exposure as data permit: AUC_{inf}, AUC_{last}, C_{max}, T_{max} and $t_{½}$.	**Part A, Part B and Part C:** • Not applicable.
Part B and Part C: • Assess the safety and tolerability of KAN-101 in participants with CeD.	**Part B and Part C:** Incidence and severity of TEAEs as assessed by the CTCAE.	**Part B and Part C:** • Not applicable.

Objectives	Endpoints	Estimands
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
Part A, Part B, and Part C: • To further characterize the PK profile of KAN-101 following multiple doses in participants with CeD. • To evaluate the immunogenicity of KAN-101.	**Part A, Part B, and Part C:** • KAN-101 PK parameters, as data permit: AUC_{inf} (dn), AUC_{last} (dn), C_{max} (dn), CL, V. • Incidence of development of ADA during the study.	• Not applicable
Part A: • Examine the biomarker response (IL-2) in peripheral blood following GC and after dosing.	**Part A:** • Change in magnitude of IL-2 response pre-and-post GC in peripheral blood at Day 15.	
Part B: • Assess the incidence of CeD symptoms before and after GC. • Assess durability of biomarker response in peripheral blood following GC.	**Part B:** • Incidence of CeD symptoms following GC as assessed by PROs including: CDSD v2.1, PGIC and PGIS. • Change in magnitude of IL-2 response pre-and-post GC in peripheral blood from baseline (run-in) to GC at Weeks 12, 24, and 36. • Change in magnitude of IL-2 response pre- and post-GC in peripheral blood from Day 15 to Weeks 12, 24, and 36.	
Part C: • Assess the incidence of CeD symptoms in participants with CeD. • Compare change in biomarker response in participants with CeD and treated with KAN-101 versus PBO. • Assess durability of biomarker (IL-2) response in peripheral blood of participants with CeD and treated with KAN-101 versus PBO.	**Part C:** • Incidence of CeD symptoms as assessed by PROs including: CDSD v2.1, PGIC and PGIS. • Change in circulating levels of IL-2 from pre-GC to post GC at Weeks 12, 24, and 36. • Change in circulating levels of of various biomarkers from pre-dose to post-dose on Day 1, 4, and 7. • Change in circulating levels of IL-2 pre- and post-GC from Day 15 to Weeks 12, 24, and 36.	
Part B and Part C Biopsy Substudy: • To evaluate the impact of KAN-101 on histology from EGD biopsy in participants with CeD.	**Part B and Part C Biopsy Substudy:** • Change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52.	

Objectives	Endpoints	Estimands
• Evaluate the potential relationship between histopathological state and response to 1 day GC.	• Correlation between histological state, symptomatic response, and biomarker responses (IL-2).	

Overall Design:

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

- **Part A** – Phase 1b, open-label, MAD study design to assess the safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years inclusive) with histology-confirmed CeD. All eligible participants will receive KAN-101.
    - Part A comprises 3 periods:
        - **Screening period:** Up to 28 days before the first dose
        - **Treatment period**: 7 days; administered IV study intervention on Day 1, Day 4, and Day 7
        - **Observation/Follow-up period**: 21 days, including post-dosing GC on Day 15 and safety follow-up visit on Day 28
        - All cohorts planned in Part A (Cohort 1: 1.2 mg/kg, Cohort 2: 3.0 mg/kg,) will employ inter-participant dosing whereby participants in each cohort will be dosed at least 14 days apart from the subsequent participants to monitor for the acute and subacute safety of KAN-101.
            - A DSMB will review cumulative safety data through the dose escalation safety review period by cohort before opening a higher dose cohort. Initiation of the next dose cohort will commence once all participants in a cohort reach Day 15 prior to the GC, and upon acceptable safety review by DSMB and approval from sponsor.
- **Part B** – Part B is a Phase 2, double-blind, PBO-controlled, parallel design study to characterize the biomarker response (plasma IL-2; primary endpoint) in peripheral blood following GC. Safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years inclusive) with histology-confirmed CeD will also be analyzed. Participants will be randomized 1:1:1:1 and stratified by participation in biopsy substudy to the following treatment groups:
    - PBO (Group 1)
    - 0.6 mg/kg (Group 2)

- 1.2 mg/kg (Group 3)
- 3.0 mg/kg (Group 4)

- Initiation of Part B will occur following the DSMB review of available safety and PK data from Part A and the sponsor's approval.
- Part B comprises 4 periods and 1 substudy:
  - **Screening period:** ≤28 days
  - **Run-in period:** 21 days; eligible participants will undergo 1-day 9g GC on first day of run-in period (at least 21 days before administration of first dose of study drug) to confirm symptomatic response to oral GC.
  - **Treatment period:** 7 days; symptomatic responders to the run-in GC will be randomized 1:1:1:1 to 1 of the 4 treatment groups and administered study intervention IV for 3 administrations (1 administration every 3 days starting at Day 1).
  - **Observation/follow-up period:** 358 days, including post-dosing GC on Day 15 (to assess primary endpoint), post-dosing GC at Weeks 12, 24 and 36 (to assess exploratory endpoints) and follow-up visits on Day 28 and Week 52.
- **Biopsy Substudy** (at applicable sites only, up to approximately 50% of Part B cohort): includes collection of duodenal biopsies at screening and Week 52.

- **Part C** – Part C is a Phase 2, double-blind, PBO-controlled, parallel design study to compare the biomarker response (plasma IL-2; primary endpoint) following GC on Day 15. Safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years inclusive) with histology-confirmed CeD will also be evaluated. Participants will be randomized 1:1:1:1 and stratified by participation in biopsy substudy to the following treatment groups:
  - PBO (Group 1)
  - 0.6 mg/kg (Group 2)
  - 1.2 mg/kg (Group 3)
  - 3.0 mg/kg (Group 4)
- Initiation of Part C will occur following the DSMB review of available safety data from Part B and the sponsor's approval.

- Part C will have 3 periods and 1 substudy:
  - **Screening period:** Day -28 to Day -1
  - **Treatment period:** Day 1 to Day 7; eligible participants will be randomized 1:1:1:1 to 1 of the 4 Treatment Groups and administered study intervention IV for 3 administrations (1 administration every 3 days starting at Day 1).
  - **Follow-up period:** Day after last dose till Day 364 (±3 days), including post-dosing GC on Day 15 (to assess primary endpoint), post-dosing GC at Weeks 12, 24 and 36 (to assess exploratory endpoints) and safety follow-up visits on Day 28 and Week 52.
- **Biopsy Substudy** (at applicable sites only, up to approximately 50% of Part C cohort): includes collection of duodenal biopsies at screening and Week 52.

Number of Participants:

Part A: up to 12 participants will be randomized.

Part B: Approximately 16 participants (approximately 4 participants per treatment group) will be randomized.

Part C: Approximately 104 participants (approximately 26 participants per treatment group) will be randomized.

Note: "Randomized" means a participant's agreement to participate in a clinical study following completion of the informed consent process, screening, and randomization.

A participant will be considered "enrolled" if the informed consent is not withdrawn prior to participating in any study activity.

Study Population:

Key inclusion and exclusion criteria are listed below.

For Part A and Part C: All inclusion/exclusion criteria must be met and confirmed prior to randomization.

For Part B: All inclusion criteria, except Inclusion Criterion #5, and all exclusion criteria must be met and confirmed prior to entry into the run-in period and GC assessment at Day 21. All inclusion criteria must be met and confirmed prior to randomization.

For Part B Biopsy Substudy: All inclusion criteria, except Inclusion Criterion #5, and all exclusion criteria must be met and confirmed prior to undergoing the screening biopsy. All inclusion/exclusion criteria must be met and confirmed prior to randomization.

For Part C Biopsy Substudy: All inclusion criteria and all exclusion criteria must be met and confirmed prior to undergoing the screening biopsy. All inclusion/exclusion criteria must be met and confirmed prior to randomization.

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Participants aged 18 years to 70 inclusive (or the minimum age of consent in accordance with local regulations) at screening.

2. Previous diagnosis of CeD, based on documentation in the source data:

   - Positive celiac serology (eg, tissue transglutaminase IgA antibody and/or deamidated DGP IgG)

     AND

   - Intestinal histology consistent with ≥ Marsh Type 2 or with evidence of villous atrophy.

3. Have HLA-DQ2.5 genotype (HLA-DQA1*05 and HLA-DQB1*02 (homozygotes or heterozygotes).

4. Negative or weak positive for transglutaminase IgA AND negative or weak positive for DGP-IgA/IgG during screening.

   - For tTG, a result of ≤10 U/mL will be considered negative or weak positive.

   - For DGP, a result of <30 U/mL will be considered negative or weak positive.

5. **Part B ONLY (prior to randomization):** Demonstrates a symptomatic response following a 1-day oral GC performed during Run-in, defined as having at least 1 moderate to severe GI symptom (either diarrhea, abdominal pain, bloating, or nausea) the day of the GC.

6. Have followed a gluten-free diet for ≥12 months immediately prior to study entry (self-reported).

Exclusion Criteria

Participants with any of the following key characteristics/conditions will be excluded:

1. Refractory CeD, defined as severe persistent or recurrent malabsorptive signs or symptoms with substantial villous atrophy (ex. Documented Marsh score 3c in source data) despite strict adherence to a GFD for at least 12 months in the absence of other disorders.
2. Selective IgA deficiency.
3. Positive for HLA-DQ8 (*DQA1*03, DQB1*0302*).
4. Known wheat allergy.
5. Known history of severe hypersensitivity reactions or anaphylaxis to gluten.
6. Previous oral GC within 12 months.
7. Active gastrointestinal disease (eg, inflammatory bowel disease, any forms of colitis, uncontrolled IBS, peptic ulcer disease, eosinophilic esophagitis, and active GI infections).
8. Previous treatment with tolerance-inducing therapies for CeD.

Study Arms and Duration:

Study Intervention(s)		
Intervention Name	KAN-101	PBO
Arm Name (group of participants receiving a specific treatment or no treatment)	**Part A:** Cohort 1 and 2 **Part B:** Group 2, 3, and 4 **Part C:** Group 2, 3, and 4	**Part A:** N/A **Part B:** Group 1 **Part C:** Group 1
Type	Drug	PBO
Dose Formulation	Solution in a single-use glass vial for dilution into saline bag for IV infusion	Solution for infusion in a saline bag
Unit Dose Strength(s)	CCI [redacted]	N/A
Dosage Level(s)	CCI [redacted]	PBO
Route of Administration	IV	IV

Study Intervention(s)		
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	Placebo
Sourcing	Provided centrally by the sponsor. Further details are presented in the IPM.	Provided locally by the site. Further details are presented in the IPM.
Packaging and Labeling	Study intervention will be provided in glass vials. Each vial will be labeled as required per country requirement. In Part B and Part C, study intervention will be blinded once diluted in a saline bag.	Study intervention will be provided in saline bags. Each saline bag will be labeled as required per country requirement. In Part B and Part C, study intervention will be blinded.

Study Arm(s)				
Part A (open-label)				
Arm Title	Cohort 1		Cohort 2	
Arm Type	Experimental		Experimental	
Arm Description	Participants will receive 1.2 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.		Participants will receive 3.0 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.	
Associated Intervention Labels	KAN-101		KAN-101	
Part B and Part C (double-blind)				
Arm Title	Group 1	Group 2	Group 3	Group 4
Arm Type	Placebo	Experimental	Experimental	Experimental
Arm Description	Participants will receive PBO IV every 3 days starting on Day 1 and ending on Day 7.	Participants will receive 0.6 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.	Participants will receive 1.2 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.	Participants will receive 3.0 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.
Associated Intervention Labels	PBO	KAN-101	KAN-101	KAN-101

In **Part A**, the decision to proceed to the next dose level of KAN-101 (either an increase or a decrease) will be made by the study team and DSMB during the dose escalation safety period. If the decision is made to dose escalate, it is the sponsor's discretion whether to proceed with escalation, expand the same dose or to modify doses based on emerging data.

In **Part B and Part C**, no dose modification is allowed following selection of doses based on safety and tolerability of doses studied in Part A.

Statistical Methods:

Sample Size Determination

It is anticipated that the study will enroll approximately 126 – 132 participants:

- Part A = 6-12 participants
- Part B = approximately 16 participants
- Part C = approximately 104 participants
- Biopsy Substudy (at applicable sites only) will enroll up to approximately 50% participants enrolled in Part B and up to approximately 50% participants enrolled in Part C.

There is no formal power calculation for the open-label Part A.

There is no formal power calculation for Part B. Descriptive summaries for primary and secondary endpoints will be reported.

In Part C, assuming the mean difference in the change from pre-GC to post-GC of the log-transformed IL-2 levels on Day 15 is 2.37 between KAN-101 and PBO and the common standard deviation is 1.53, a sample size of 26 in each group will have 99% power, using a 2-group t-test with a 5%, 2-sided significance level. The Part C sample size is large enough to offer insight into the exploratory endpoints.

Primary Endpoint Analysis

For Part A, the primary endpoint is incidence and severity of TEAEs as assessed by CTCAE.

For Part B, the primary endpoint is change in magnitude of IL-2 response pre- and post-GC in peripheral blood from baseline screening to Day 15.

For Part C, the primary endpoint is the change in IL-2 from pre-GC to post-GC on Day 15 in participants treated with KAN-101 versus PBO.

Main Analytical Approach:

- **For Part A**, number and percent of participants with TEAEs will be summarized by cohort, SOC, PT, and severity.
- **For Part B,** the primary endpoint will be descriptively summarized by treatment using Estimand 1 for FAS. There is no statistical hypothesis testing.
- **For Part C**, change in IL-2 from pre-GC to post-GC on Day 15 will be analyzed using ANOVA model.
    - The main analysis of the primary endpoint will be based on Estimand 2 using FAS. The LSM difference of the change from pre-GC to post-GC on Day 15 (log transformed) between each KAN-101 group and PBO will be provided; prohibited medications, incomplete GC at Day 15, and discontinuation of study intervention are intercurrent events. All data collected after any intercurrent events will be excluded.
    - All statistical tests will be 2-tailed at a $\alpha = 0.05$.

Secondary Endpoint Analysis

For Part A, PK concentration and PK parameters will be descriptively summarized by treatment group.

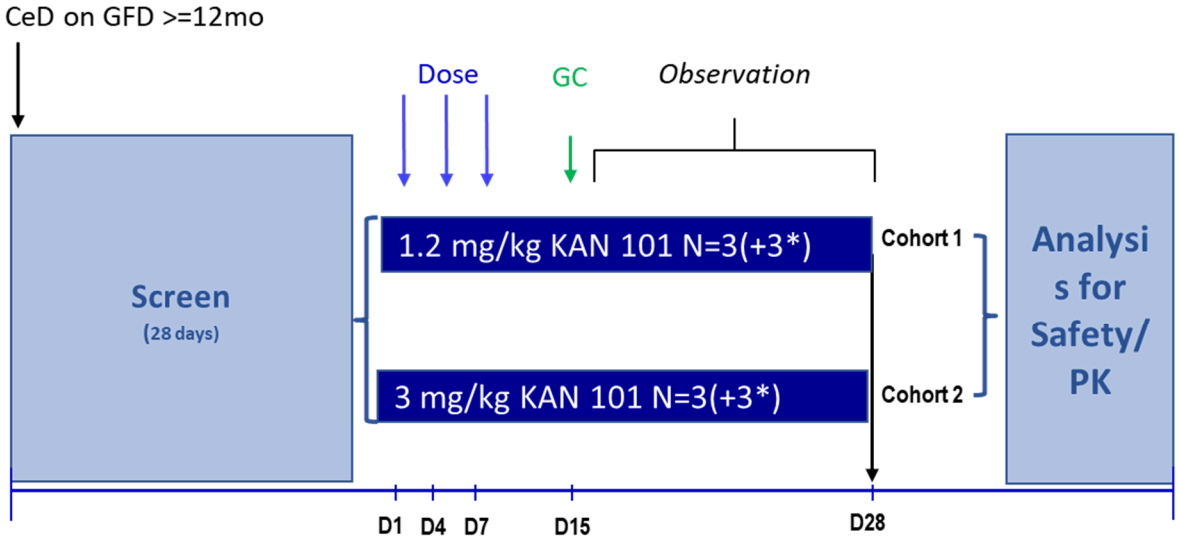
For Part B and Part C, number and percent of participants with TEAEs will be summarized by treatment, SOC, PT, and severity. PK concentration and PK parameters will be descriptively summarized by treatment group. Number of TEAEs (all-causality and treatment-related) and percent of participants with TEAEs will also be summarized by treatment period, treatment, SOC, PT, and severity.

Ethical Considerations:

The overall potential benefit/risk of KAN-101 is considered favorable. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with KAN-101 are justified by the anticipated benefits that may be afforded to participants with CeD.

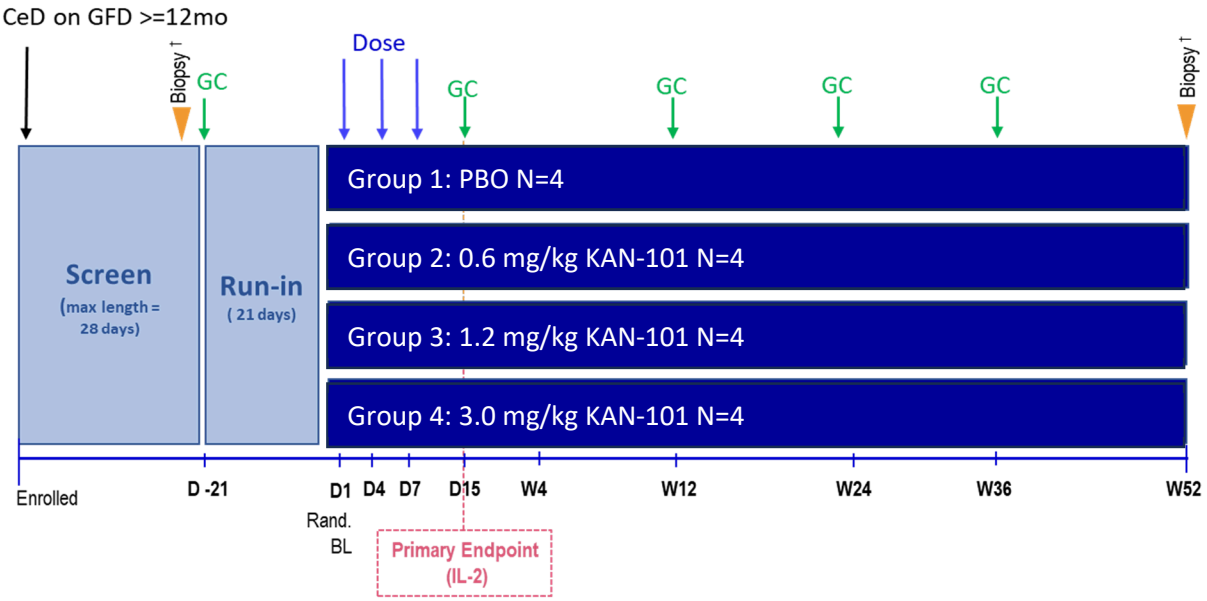
1.2. Schema

1.2.1. Part A Study Design Schema



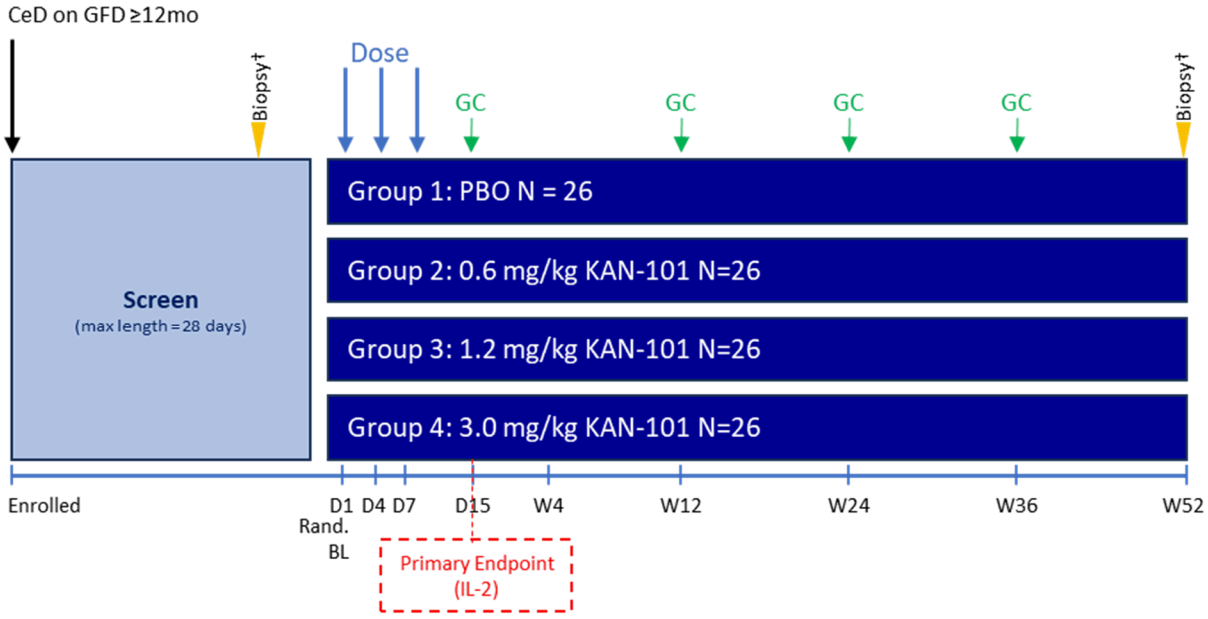
* Depending on safety and tolerability, each group may enroll 3 additional participants to establish the MTD.

1.2.2. Part B Study Design Schema



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

1.2.3. Part C Study Design Schema



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

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Part A (Phase 1b – Open-Label)

Visit Identifier	Screen	Treatment Period			GC	FU	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Up to Day -1** (max length of screening is 28 days)	**Day 1**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**ET**	• Day relative to start of study intervention (Day 1). • FU visit must occur between Day 25 and Day 31.
Visit Window						**(± 3 d)**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Screening Assessments								• All screening should be done ≤28 days before the first dose.
Informed consent	X							• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Demographics and medical history	X							• Includes disease history (symptoms at diagnosis and length of time on GFD).
Review eligibility criteria	X	X						
HIV, HBV, HCV testing	X							
HLA genotype and CeD serology	X							• All participants will be assessed via central laboratory for HLA genotype and CeD serology (eg, tTG-IgA and DGP-IgG) at screening. • For rescreening: HLA does not need to be repeated and CeD serology only needs to be repeated if >3 months have elapsed from last assessment.
12-Lead ECG	X							• Not required for participants who have had an ECG within 12 weeks prior to screening.

Visit Identifier	Screen	Treatment Period			GC	FU	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Up to Day -1** (max length of screening is 28 days)	**Day 1**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**ET**	• Day relative to start of study intervention (Day 1). • FU visit must occur between Day 25 and Day 31.
Visit Window						**(± 3 d)**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Clinical Procedures								
Physical examination	X					X	X	• See Section 8.3.5 for additional information. • Includes weight and height at screening only.
Vital signs	X	X	X	X	X	X	X	• See Section 8.3.2 for additional information. • Includes weight and height at screening only.
Contraception check	X	X	X	X	X	X	X	
Laboratory Assessments								• See Section 8.3.4 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
Safety laboratory tests	X	X	X	X	X	X	X	• Includes hematology, blood chemistry, and urinalysis. • Days 1, 4, and 7: Samples/measurements taken pre-dose (at least 5 minutes prior to infusion). • Day 15: Collected prior to GC.
Pregnancy test	X	X	X	X	X	X	X	• Pregnancy test at screening must be serum; serum or urine tests are acceptable any day after screening. • Pregnancy test required if WOCBP has a missed period. • Pregnancy test must be negative before study intervention or GC is administered
Study Intervention and Other Treatments								• See Section 6 for additional information.
Study intervention administration		X	X	X				• See Section 6.1 for additional information.
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	• See Section 6.9 for additional information.
Incidental gluten exposure	→	→	→	→	→	→	→	• Collected daily (→) as part of eDiary and reviewed at scheduled visits.
Gluten Challenge					X			• Participants who withdraw from treatment and do not receive 3 full doses should not receive GC (see Section 8.2.1).

Visit Identifier	Screen	Treatment Period			GC	FU	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Up to Day -1** (max length of screening is 28 days)	**Day 1**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**ET**	• Day relative to start of study intervention (Day 1). • FU visit must occur between Day 25 and Day 31.
Visit Window						**(± 3 d)**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Efficacy Assessments								• See Section 8 for additional information.
CDSD© v2.1 self-administered by participant at home	→	→	→	→	→	→	X	• Completed daily (→) from time of consent to Day 28; should be completed for at least a minimum of 7 consecutive days during screening at any time prior to the baseline visit (Day 1). • For re-screening: PRO only needs to be repeated if >3 months have elapsed from end of last PRO administration (and may not include the GC day).
PGIS		X			X	X	X	
PGIC					X	X	X	
PK/Immunogenicity Assessments								
PK blood sample		X		X			X	• PK sampling will be done pre-dose (at least 5 minutes prior to infusion) and end of infusion (+2) minutes. Additional sampling will be done at 45 (±2) minutes, 1 hour (±5 minutes), 1.5 hour (± 5 minutes), 2.5 hours (±5 minutes), 4.5 hours (±5 minutes) and 7 hours (±5 minutes) after infusion start. • An ET PK sample is required if ET visits is within 1 week of the last dose.
ADA sample		X		X		X	X	• On dosing days, samples collected pre-dose (at least 5 minutes prior to infusion).
Safety Assessments								• See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	• See Section 8.4 for additional information.
Biomarker Assessments								• See study laboratory manual.
PBMC sample		X			X			• Day 1: sample collected pre-dose (at least 5 minutes prior to infusion). • Day 15: sample collected prior to GC.

Visit Identifier	Screen	Treatment Period			GC	FU	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Up to Day -1** (max length of screening is 28 days)	**Day 1**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**ET**	• Day relative to start of study intervention (Day 1). • FU visit must occur between Day 25 and Day 31.
Visit Window						**(± 3 d)**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Plasma IL-2 biomarker		X	X	X	X			• See Section 8.2 for additional information. • Samples are collected pre dose (at least 5 minutes prior to dose) and 4 hours (± 5 minutes) post dose on Day 1, 4 and 7. • Samples are collected pre-GC (at least 5 minutes prior to GC) and 4 hours (± 15 minutes) post GC on Day 15. • Day 15: Participants who withdraw from treatment and do not receive 3 full doses should not have plasma samples collected.

1.3.2. Part B (Phase 2 – Double-Blind)

Visit Identifier	Screen	Run-in		Treatment Period			GC	FU W4	GC W12	GC W24	GC W36	FU W52	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	Day -49 to Day -22 (fasted)	Day -21 (fasted)	Day -20 to Day -1	Day 1 (fasted)	Day 4	Day 7	Day 15 (fasted)	Day 28	Day 84 (fasted)	Day 168 (fasted)	Day 252 (fasted)	Day 364		• Day relative to start of study intervention (Day 1). • Run-in is a 1-day GC visit and must be at least 21 days prior to Day 1.
Visit Window		**-3 d**						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Screening Assessments														• All screening should be done ≥21 days and ≤49 days before the first dose.
Informed consent	X													• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Demographics and medical history	X													• Includes disease history (symptoms at diagnosis and length of time on GFD).
Review eligibility criteria	X	X		X										
HIV, HBV, HCV testing	X													
HLA genotype and CeD serology	X													• All participants will be assessed via central laboratory for HLA genotype and CeD serology (eg, tTG-IgA and DGP-IgG) at screening to confirm eligibility prior to screening GC. • For rescreening: HLA does not need to be repeated and CeD serology only needs to be repeated if >3 months have elapsed from last assessment.
12-Lead ECG	X													• Not required for participants who have had an ECG within 12 weeks prior to screening.
Clinical Procedures														
Physical examination	X											X	X	• See Section 8.3.1 for additional information.
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X	• See Section 8.3.2 for additional information. • Includes weight and height at screening only.
Contraception check	X	X		X	X	X	X	X					X	

Visit Identifier	Screen	Run-in		Treatment Period			GC	FU W4	GC W12	GC W24	GC W36	FU W52	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Day -49 to Day -22 (fasted)**	**Day -21 (fasted)**	**Day -20 to Day -1**	**Day 1 (fasted)**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364**		• Day relative to start of study intervention (Day 1). • Run-in is a 1-day GC visit and must be at least 21 days prior to Day 1.
Visit Window		**-3 d**						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Laboratory Assessments														• See Section 8.3.4 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the study laboratory manual.
Safety laboratory tests	X			X			X		X	X	X	X	X	• Includes blood chemistry, hematology, and urinalysis. • At least 8 hours fasting is required before collecting samples for safety laboratory tests (see Section 8.3.4). • Samples/ measurements taken pre-dose (at least 5 minutes prior to infusion). • Collected prior to GC.
Pregnancy test	X	X		X	X	X	X	X	X	X	X		X	• Pregnancy test at screening must be serum; serum or urine tests are acceptable on dosing days (Day 1, 4, and 7). • Pregnancy test must be negative before study intervention or GC is administered. May also perform urine pregnancy test prior to EGD per local practice guidelines • ET: Only needed if ET occurs up to Day 28.
Study Intervention and Other Treatments														• See Section 6 for additional information.
Study intervention administration				X	X	X								• See Section 6.1 for additional information.
Prior/concomitant treatment(s)	X	X		X	X	X	X	X	X	X	X	X	X	• See Section 6.9 for additional information.

Visit Identifier	Screen	Run-in		Treatment Period			GC	FU W4	GC W12	GC W24	GC W36	FU W52	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Day -49 to Day -22 (fasted)**	**Day -21 (fasted)**	**Day -20 to Day -1**	**Day 1 (fasted)**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364**		• Day relative to start of study intervention (Day 1). • Run-in is a 1-day GC visit and must be at least 21 days prior to Day 1.
Visit Window		**-3 d**						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
EGD with biopsy (Substudy Only)	X											X		• For participants in Biopsy Substudy Only. • The EGD with biopsy will be performed once all other inclusion criteria, except for the criteria around symptoms following GC, are fulfilled. • Biopsy must be collected at least 4 days prior to run-in GC. • Approximately 6 duodenal biopsies. • For rescreening: EGD with biopsy does not need to be repeated unless >3 months have elapsed from last assessment.
Gluten Challenge		X					X		X	X	X			• See Section 8.2.1for additional information. • During the run-in period: 1-day GC on site by patients ≥3 weeks before the first administration of study intervention (Day 1). • Participants who withdraw from treatment and do not receive 3 full doses should not receive GC.
Efficacy Assessments														• See Section 8 for additional information.
Plasma IL-2 biomarker		X					X		X	X	X			• See Section 8.2.1 for additional information. • At every GC, plasma IL-2 sample should be collected at least 5 minutes before and 4 hours (± 15 minutes) after GC. • Participants who withdraw from treatment and do not receive 3 full doses should not have plasma samples collected.

Visit Identifier	Screen	Run-in		Treatment Period			GC	FU W4	GC W12	GC W24	GC W36	FU W52	ET	Notes
Abbreviations used in this table may be found in Appendix 13.	**Day -49 to Day -22 (fasted)**	**Day -21 (fasted)**	**Day -20 to Day -1**	**Day 1 (fasted)**	**Day 4**	**Day 7**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364**		• Day relative to start of study intervention (Day 1). • Run-in is a 1-day GC visit and must be at least 21 days prior to Day 1.
Visit Window		**-3 d**						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
CDSD© v2.1 self-administered by participant at home	X	→		→	→	→	→	→	→	→	→	→	X	• Completed daily (→) from time of consent to Week 52; CDSD v2.1 should be completed for at least a minimum of 7 consecutive days during screening at any time prior to run-in GC visit (Day -21) for Part B. • For re-screening: CDSD v2.1 only needs to be repeated if >3 months have elapsed from end of last PRO administration (and may not include the GC day).
Incidental gluten exposure check		→		→	→	→	→	→	→	→	→	→	X	• Included in the daily (→) eDiary and reviewed at study visits.
PGIS				X			X	X	X	X	X	X	X	
PGIC							X	X	X	X	X	X	X	
PK/ Immunogenicity Assessments														
PK blood sample				X		X							X	• PK sampling collected pre-dose (at least 5 minutes prior to infusion) and end of infusion (+2) minutes. Additional sampling will be done at 2.5 hours (±5 minutes) and 4 hours (±5 minutes) after infusion start. • An ET PK sample is required if ET visits is within 1 week of the last dose.
ADA sample				X		X		X	X	X	X	X	X	• On dosing days, samples collected pre-dose (at least 5 minutes prior to infusion).
Safety Assessments														• See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	X		X	X	X	X	X	X	X	X	X	X	• See Section 8.4 for additional information.

1.3.3. Part C (Phase 2 – Double-Blind)

Visit Identifier	Screen	Treatment Period			Follow-Up Period						ET	Notes
					GC	FU W4	GC W12	GC W24	GC W36	FU W52		
Abbreviations used in this table may be found in Appendix 13.	**Day -28 to Day-1**	**Day 1 (fasted)**	**Day 4 (fasted)**	**Day 7 (fasted)**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364 (fasted)**		• Day relative to start of study intervention (Day 1).
Visit Window						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Screening Assessments												
Informed consent	X											• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Demographics and medical history	X											• Includes disease history (symptoms at diagnosis and length of time on GFD).
Review eligibility criteria	X	X										
HIV, HBV, HCV testing	X											
HLA genotype and CeD serology	X											• All participants will be assessed via central laboratory for HLA genotype and CeD serology (eg, tTG-IgA and DGP-IgG) at screening to confirm eligibility prior to screening GC. • For rescreening: HLA does not need to be repeated and CeD serology only needs to be repeated if >3 months have elapsed from last assessment.
12-Lead ECG	X											• Not required for participants who have had an ECG within 12 weeks prior to screening.
Clinical Procedures												
Physical examination	X									X	X	• See Section 8.3.1 for additional information.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	• See Section 8.3.2 for additional information. • Includes weight and height at screening only.
Orthostatic vital signs, oral temperature and RR		X	X	X								• See Section 8.3.2.1 for additional information. • To be measured pre-dose and at approximately 45 mins, 2 hours, and then, every 2 hours (until discharge) post end-of-infusion. • Additional measurements may be taken in case of treatment-emergent, clinically significant orthostatic hypotension or syncope. See Section 8.3.2.
Contraception check	X	X	X	X	X	X					X	

Visit Identifier	Screen	Treatment Period			Follow-Up Period						ET	Notes
					GC	FU W4	GC W12	GC W24	GC W36	FU W52		
Abbreviations used in this table may be found in Appendix 13.	**Day -28 to Day-1**	**Day 1 (fasted)**	**Day 4 (fasted)**	**Day 7 (fasted)**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364 (fasted)**		• Day relative to start of study intervention (Day 1).
Visit Window						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
Laboratory Assessments												• See Section 8.3.4 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the study laboratory manual.
Safety laboratory tests	X	X	X	X	X		X	X	X	X	X	• Includes blood chemistry, hematology, and urinalysis pre-dose/GC (approximately 5 minutes before) collection (after at least 8 hours fast) (see Section 8.3.4). • Additional safety labs (hematology and chemistry) may be collected in case of treatment emergent, clinically significant, orthostatic hypotension, syncope or treatment-related TEAE of Grade 3 or above (see Section 8.3.4).
Pregnancy test	X	X	X	X	X	X	X	X	X		X	• Pregnancy test at screening must be serum; serum or urine tests are acceptable on dosing days (Days 1, 4, and 7). • Pregnancy test must be negative before study intervention or GC is administered. May also perform urine pregnancy test prior to EGD per local practice guidelines. • ET: Only needed if ET occurs up to Day 28.
Study Intervention and Other Treatments												• Study Intervention and Other Treatments.
Study intervention administration		X	X	X								• See Section 6.1 for additional information.
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	X	X	X	X	• See Section 6.9 for additional information.

Visit Identifier	Screen	Treatment Period			Follow-Up Period						ET	Notes
					GC	FU W4	GC W12	GC W24	GC W36	FU W52		
Abbreviations used in this table may be found in Appendix 13.	**Day -28 to Day-1**	**Day 1 (fasted)**	**Day 4 (fasted)**	**Day 7 (fasted)**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364 (fasted)**		• Day relative to start of study intervention (Day 1).
Visit Window						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
EGD with biopsy (Substudy Only)	X									X		• For participants in Biopsy Substudy Only. • The EGD with biopsy will be performed once all other inclusion criteria are met. • Biopsy must be collected at least 4 days prior to dosing (Day 1). • Approximately 6 duodenal biopsies. • For rescreening: EGD with biopsy does not need to be repeated unless >3 months have elapsed from last assessment.
Gluten Challenge					X		X	X	X			• See Section 8.2.1 for additional information. • Participants who withdraw from treatment and do not receive 3 full doses should not receive GC.
PD Assessments												• See Section 8 for additional information.
Plasma IL-2 biomarker					X		X	X	X			• See Section 8.2.2 for additional information. • At every GC visit, plasma IL-2 sample should be collected at least 5 minutes before and 4 hours (± 15 minutes) after GC. • Participants who withdraw from treatment and do not receive 3 full doses should not have plasma samples collected.
Other plasma biomarkers		X	X	X								• See Section 8.7 for additional information. • At every dosing visit, plasma samples should be collected at least 5 minutes before and 4 hours (±15 minutes) after dosing. • Additional plasma samples should be collected as soon as practically feasible, in an event of treatment emergent, clinically significant orthostatic hypotension, syncope, or treatment-related TEAE, Grade 3 or above. • Participants who withdraw from treatment and do not receive 3 full doses should not have plasma samples collected.

Visit Identifier	Screen	Treatment Period			Follow-Up Period						ET	Notes
					GC	FU W4	GC W12	GC W24	GC W36	FU W52		
Abbreviations used in this table may be found in Appendix 13.	**Day -28 to Day-1**	**Day 1 (fasted)**	**Day 4 (fasted)**	**Day 7 (fasted)**	**Day 15 (fasted)**	**Day 28**	**Day 84 (fasted)**	**Day 168 (fasted)**	**Day 252 (fasted)**	**Day 364 (fasted)**		• Day relative to start of study intervention (Day 1).
Visit Window						**±3 d**	**±5 d**	**±5 d**	**±5 d**	**±3 d**		• See Section 8.4.3 for follow-up AE and SAE assessments.
CDSD© v2.1 self-administered by participant at home	X	→	→	→	→	→	→	→	→	X	X	• CDSD v2.1 should be completed for at least a minimum of 7 consecutive days during screening. • For re-screening: CDSD v2.1 only needs to be repeated if >3 months have elapsed from end of last PRO administration.
Incidental gluten exposure check		→	→	→	→	→	→	→	→	X	X	• Included in the daily eDiary and reviewed at study visits.
PGIS		X			X	X	X	X	X	X	X	
PGIC					X	X	X	X	X	X	X	
PK/ Immunogenicity Assessments												
PK blood sample		X		X							X	• PK sampling collected pre-dose (at least 5 minutes prior to infusion) and end of infusion (+2) minutes. Additional sampling will be done at 2.5 hours (±5 minutes) and 4 hours (±5 minutes) after infusion start. • An ET PK sample is required if ET visits is within 1 week of the last dose.
ADA sample		X		X		X	X	X	X	X	X	• On dosing days, samples collected pre-dose (at least 5 minutes prior to infusion).
Safety Assessments												• See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	X	X	• See Section 8.4 for additional information.

2. INTRODUCTION

2.1. Study Rationale

The purpose of the study is to evaluate the safety, tolerability, PK parameters, and plasma biomarker (IL-2) response of participants with CeD treated with KAN-101.

2.2. Background

2.2.1. 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 et al, 2006) (Rubio-Tapia et al, 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 et al, 2001; Green & Jabri, 2006).

It has been recently estimated that 0.7% of the world-wide population has CeD, with global prevalence rates on the rise (Singh et al, 2018). CeD is strongly associated with the Human Leukocyte Antigen *(HLA)-DQA1* and *HLA-DQB1* loci (*HLA-1*05*, *HLA-DQB1*02*; commonly referred to as HLA-DQ2.5) which is present in approximately 90% of CeD patients (Sollid et al, 1989; Sollid et al, 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 & Jabri, 2013). Diagnosis is typically made by a combination of positive IgA, tTG, and/or IgG, DGPs, and small intestinal biopsy demonstrating villous abnormalities while on a gluten-containing diet or following a GC (Halfdanarson et al, 2006; Rubio-Tapia et al, 2013).

There is currently no pharmaceutical treatment approved for the management of CeD. Patients manage their symptoms by strict adherence to a GFD, which often presents a substantial logistical and financial burden (See et al, 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 et al, 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.

2.2.2. KAN-101

KAN-101 is composed of a synthetic liver-targeting CCI [redacted] to a synthetic CCI [redacted] 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 IV infusion.

KAN-101 harnesses natural tolerogenic pathways in the liver (Thomson & Knolle, 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 proposed mechanism of action of KAN-101 is receptor-mediated internalization of the molecule into liver cells, and the induction of immune tolerance through subsequent KAN0009 gliadin peptide antigen presentation on the major histocompatibility complex (MHC; class I and II). After KAN-101 internalization into liver cells, the KAN0009 peptide is released from the GP portion and processed intracellularly for presentation by MHC and signaling to gliadin-specific T cells for the induction of immune tolerance and subsequent amelioration of gut pathology.

The mechanisms by which KAN-101 induces immunologic tolerance are mediated by:

- 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

For more information on the nonclinical findings, please see the KAN-101 IB.

2.2.3. Clinical Overview

KAN-101 was evaluated in a FIH Phase 1 study in patients with CeD on a GFD (KAN-101-01). This was a 2-part, multicenter study designed to examine the safety and tolerability of SAD (Part A) and MAD (Part B) of KAN-101. A total of 41 participants received at least 1 dose of KAN-101 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg, and 1.5 mg/kg) during the study.

In Study KAN-101-01 administration of KAN-101 was effective at inducing T-cell tolerance:

- Three doses of KAN-101, administered 3 days apart, at 0.15, 0.3 and 0.6 mg/kg dose levels was effective in inducing T cell tolerance to gliadin. KAN-101 treated patients exhibited minimal change or a decrease in the gliadin-specific T-cell response following GC while placebo patients exhibited an increase in the gliadin-specific T-cell response following GC.
- KAN-101 also modified the immediate immune reaction upon ingestion of gluten by CeD patients in a dose-dependent manner. Patients treated with 3 doses of 0.6 mg/kg KAN-101, administered 3 days apart, exhibited lower median plasma IL-2 levels

within hours of GC compared to placebo or 0.15 and 0.3 mg/kg KAN-101 dose levels.

KAN-101 demonstrated an acceptable safety and tolerability profile after single and multiple doses at all dose levels tested in the KAN-101-01 study. There were no deaths, SAEs, Grade 3 TEAEs, or DLTs observed. TEAEs were consistent with CeD patients upon gluten ingestion (ie, nausea, emesis, abdominal pain, headache, and diarrhea). No clinically relevant trends were observed for changes in vital signs, physical examination, laboratory tests, or ECG results. There were no meaningful correlations between the frequency of TEAEs and study drug dose level. There was an increased frequency of subjects who experienced GI AEs in the total drug-treated group than in the placebo group. No MTD of KAN-101 was identified in KAN-101-01 and no meaningful safety differences were observed among treatment groups during the study.

Preliminary data from the KAN-101-01 study suggests rapid elimination with mean half-life ranging from 3.74 to 36.8 minutes across 0.15 mg/kg to 1.2 mg/kg doses, following single or repeat IV infusions of KAN-101. The mean KAN-101 maximum exposure (C_{max}) and systemic exposure (AUC) appeared to exhibit approximate dose proportionality across 0.15 to 1.2 mg/kg dose range. With repeat dosing, there was no accumulation of KAN-101 which was in concordance with the rapid elimination.

In KAN-101-01 study, 3 doses of KAN-101 0.15 mg/kg, 0.3 mg/kg and 0.6 mg/kg given every 3 days exhibited minimal changes or a decrease in the gliadin-specific T-cell response compared to placebo that exhibited an increased T-cell response following GC. In addition, 3 doses of KAN-101 0.6 mg/kg lowered median IL-2 levels after GC compared to the IL-2 levels in Placebo or 0.15 mg/kg and 0.3 mg/kg KAN-101 groups. For more information on the nonclinical and previous clinical findings, please see the KAN-101 IB.

Based on nonclinical and clinical findings from the FIH study (KAN-101-01), the sponsor is initiating this Phase 1b/2 study of KAN-101 in adult participants with CeD.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of KAN-101 may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [KAN-101 and PBO]		
Potential for exacerbation of gastrointestinal symptoms associated with CeD, which may include and are not necessarily limited to AEs of headache, dizziness, fatigue/lethargy, nausea, vomiting, abdominal pain, diarrhea, constipation, skin rash, and abdominal tenderness.	The potential risks are based on the mechanism of action of KAN-101 and other similar therapeutic investigational immunomodulatory therapies in CeD (Daveson et al, 2017; Truitt et al, 2019).	AEs and clinical laboratory results will be monitored on an ongoing basis and managed according to established standard of care.
Use of a placebo arm in Part B and Part C.	The use of a placebo represents a potential risk.	Participants who experience worsening of CeD may discontinue from the study and may receive SOC treatment at the investigator's discretion.
IV infusions will be administered over 30 minutes every 3 days during study treatment period.	IRR are known risks associated with IV infusions.	IRR will be monitored and specific guidance on acute and prophylactic treatment of IRRs and recommendations for future infusions of KAN-101 are provided in Appendix 9.
Potential hypersensitivity reactions may occur and include skin reaction, mucosal tissue reaction, respiratory reaction, GI reactions, and CV reactions.	Similar to other biologic molecules.	Participants will be closely monitored on site for 4 hours post infusion for signs of any reaction.
KAN-101 is a liver targeting agent.	Although FIH Study KAN-101-01 and nonclinical data show that KAN-101 had no significant impact on the liver (eg, liver enzyme levels and histopathology), KAN-101's potential impact on liver enzymes will continue to be evaluated in the clinical setting.	Transaminase levels will be closely monitored and are included in safety laboratory assessments. Participants with ALT, AST, or ALP > 1.5 x ULN are not eligible for enrollment in KAN-101-02. Participants considered to have a potential case of Hy's law will lead to a cessation of clinical dosing and participant will be followed to resolution.
Study Procedures		
KAN-101-02 includes a single 1-day GC (9 g gluten) in Part A, up to five 1-day GC (9 g gluten)	Known AEs associated with GC are expected, which may include and are not necessarily limited	Participants will consume the GC in clinic and will be monitored for AEs associated with GC and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
in Part B, and up to four 1-day GC (9 g gluten) in Part C.	to AEs of headache, dizziness, fatigue/lethargy, nausea, vomiting, abdominal pain, diarrhea, constipation, skin rash, and abdominal tenderness.	managed according to established standard of care.
KAN-101-02 Part B and Part C include a biopsy substudy with 2 EGD with biopsy.	EGD with biopsy carries a small risk of bowel perforation. Duodenal biopsies also carry the risk of duodenal hematoma.	EGD for the study will be performed by qualified and experienced gastroenterologists.
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific screening procedures and assessments per local requirements.
Enrollment of non-GC responders into the Part B study may confound study primary endpoint.	Results could potentially be confounded by non-symptomatic participants.	Eligibility criteria and a pre-randomization GC are required to ensure that symptomatic participants are randomized.

2.3.2. Benefit Assessment

There is no individual health benefit for participating in the study. However, participants contribute to the process of developing new therapies for CeD for which there remains a strong unmet medical need for pharmacologic interventions to help alleviate the growing disease burden.

2.3.3. Overall Benefit/Risk Conclusion

The overall potential benefit/risk of KAN-101 is considered favorable.

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with KAN-101 are justified by the anticipated benefits that may be afforded to participants with CeD.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
Part A: • Assess the safety and tolerability of KAN-101 in participants with CeD.	**Part A:** • Incidence and severity of TEAEs as assessed by CTCAE.	**Part A:** • Not applicable.
Part B: • Examine the biomarker response (IL-2) in peripheral blood following GC and after dosing.	**Part B:** • Change in magnitude of IL-2 response pre-and post-GC in peripheral blood from baseline screening to Day 15.	**Part B:** **Estimand 1:** This estimand is a treatment policy, observed data will be used for summary without regard to intercurrent events. It includes the following 5 attributes: Population: Participant with celiac disease as defined by the Part B inclusion and exclusion criteria. Variable: Change in magnitude of IL-2 response pre- and post-GC from baseline to Day 15. Treatment conditions: 3 dose groups of KAN-101 or PBO. Intercurrent Events: Intercurrent events will not be considered for analysis. Population level summary: Mean, geometric mean ratio of post-GC vs pre-GC in IL-2 at Day -21 and Day 15 by treatment.
Part C: • Compare change in biomarker (IL-2) response following GC in participants with CeD treated with KAN-101 versus PBO.	**Part C:** • Change in levels of IL-2 from pre-GC to post-GC on Day 15.	**Part C:** **Estimand 2:** The primary estimand is the hypothetical estimand, which estimates the treatment effect of KAN-101 vs PBO for IL-2 under the scenario of no intercurrent events. It includes the following 5 attributes:Population: Participant with celiac disease as defined by

Objectives	Endpoints	Estimands
		the Part C inclusion and exclusion criteria. Variable: log transformed IL-2 change from pre-GC to post-GC on Day 15. Treatment conditions: 3 dose groups of KAN-101 or PBO. Intercurrent Events: Prohibited medication, incomplete GC on Day 15, and discontinuation of study intervention. All data collected after any intercurrent events will be excluded. Population level summary: The LSM difference of the change from pre-GC to post-GC (log transformed) between each KAN-101 group and PBO.
Secondary:	**Secondary:**	**Secondary:**
Part A, Part B and Part C: • Assess the PK of multiple doses of KAN-101 in participants with CeD. **Part B and Part C:** • Assess the safety and tolerability of KAN-101 in participants with CeD.	**Part A, Part B and Part C:** • KAN-101 plasma exposure as data permit: AUC_{inf}, AUC_{last}, C_{max}, T_{max} and $t_{½}$. **Part B and Part C:** Incidence and severity of TEAEs as assessed by the CTCAE.	**Part A, Part B and Part C:** • Not applicable. **Part B and Part C:** • Not applicable.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
Part A, Part B, and Part C: • To further characterize the PK profile of KAN-101 following multiple doses in participants with CeD. • To evaluate the immunogenicity of KAN-101. **Part A:** • Examine the biomarker response (IL-2) in peripheral blood following GC and after dosing. **Part B:** • Assess the incidence of CeD symptoms before and after GC. • Assess durability of biomarker response in peripheral blood following GC.	**Part A, Part B, and Part C:** • KAN-101 PK parameters, as data permit: AUC_{inf} (dn), AUC_{last} (dn), C_{max} (dn), CL, V • Incidence of development of ADA during the study. **Part A:** • Change in magnitude of IL-2 response pre-and-post GC in peripheral blood at Day 15. **Part B:** • Incidence of CeD symptoms following GC as assessed by PROs including: CDSD v2.1, PGIC and PGIS. • Change in magnitude of IL-2 response pre-and-post GC in peripheral blood from baseline (run-in) to GC at Weeks 12, 24, and 36. • Change in magnitude of IL-2 response pre- and post-GC in	• Not applicable

Objectives	Endpoints	Estimands
	peripheral blood from Day 15 to Weeks 12, 24, and 36.	
Part C: • Assess the incidence of CeD symptoms in participants with CeD.	**Part C:** • Incidence of CeD symptoms as assessed by PROs including: CDSD v2.1, PGIC and PGIS.	
• Compare change in biomarker response in participants with CeD and treated with KAN-101 versus PBO.	• Change in circulating levels of IL-2 from pre-GC to post GC at Weeks 12, 24, and 36. • Change in circulating levels of various biomarkers from pre-dose to post-dose on Day 1, 4, and 7.	
• Assess durability of biomarker (IL-2) response in peripheral blood of participants with CeD and treated with KAN-101 versus PBO.	• Change in circulating levels of IL-2 pre- and post-GC from Day 15 to Weeks 12, 24, and 36.	
Part B and Part C Biopsy Substudy: • To evaluate the impact of KAN-101 on histology from EGD biopsy in participants with CeD.	**Part B and Part C Biopsy Substudy:** • Change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52.	
• Evaluate the potential relationship between histopathological state and response to 1 day GC.	• Correlation between histological state, symptomatic response, and biomarker responses (IL-2).	

4. STUDY DESIGN

4.1. Overall Design

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

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

Anokion as the sponsor of the study, is delegating to Pfizer all obligations for conduct of Study, including responsibility for preparing the protocol, and overall conduct and oversight of the study, including contracting with study sites. Kanyos Bio, Inc. is a wholly owned subsidiary of Anokion.

4.1.1. Part A: Phase 1b, Open-Label, Multiple Ascending Dose Study

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

Part A comprises 3 periods:

- **Screening period:** Up to 28 days before the first dose
- **Treatment period:** 7 days
    - Eligible participants will be administered IV study intervention on Day 1, Day 4, and Day 7 (see Section 6.1.1).
        - Post infusion, participants will be monitored in the clinic for 4 hours for infusion-related reactions (see Appendix 9).
    - The dose cohorts planned for Part A are:
        - 1.2 mg/kg (Cohort 1)
        - 3.0 mg/kg (Cohort 2)
        - Based on emerging data from previous and ongoing cohorts, doses planned may be repeated, modified and other doses may be explored in additional cohorts. If the exposures in the subsequent dose are projected to exceed the exposure limits pre-specified, that dose will not be explored.
- **Observation/Follow-up period:** 21 days
    - **Post-dosing GC on Day 15**: All participants administered KAN-101 will return to the clinic on Day 15 to receive a 1-day 9g oral GC to assess exploratory endpoints (plasma IL-2 biomarker response to gluten and collect symptom information).
    - **Safety follow-up visit on Day 28**: includes assessment of AEs, clinical signs and symptoms, and review of clinical laboratory values.

4.1.1.1. Part A Multiple Dose Escalation

All cohorts in Part A will employ inter-participant dosing whereby participants in each cohort will be dosed at least 14 days apart from the subsequent participants to monitor for the acute and subacute safety of KAN-101.

For Part A, a DSMB (see Section 10.1.5) will review cumulative safety data through the dose escalation safety review period (see Section 4.1.1.1.2) by cohort before opening a higher dose cohort. Initiation of the next dose cohort will commence once all participants in a cohort reach Day 15 prior to the GC, and upon acceptable safety review by DSMB and approval from sponsor.

Participants who withdraw from the study may be replaced at the discretion of the sponsor. A replacement subject will receive the same treatment as the withdrawn participant.

4.1.1.1.1. Dose-Limiting Toxicities (Part A Only)

- Dose-limiting toxicity will be defined as any Grade 2 AE lasting longer than 14 days or any ≥ Grade 3 AE assessed as related to study intervention.
- If a DLT is observed in Part A, the study will be paused and the DSMB will review the information prior to dosing additional participants. The cohort will be expanded to 6 participants total before dose escalation is reviewed.
- The NTD is the dose level at which 2 or more participants experience a DLT during the dose escalation safety review period. The MTD will be defined as the dose level immediately below the NTD.
    - Of note, dose escalation may not identify an NTD or MTD.
    - If an MTD is identified in Part A, dose levels in Part B will not exceed the MTD.

DLTs DO NOT include:

- AEs attributable solely to intercurrent illness or other concomitant medications.

Stopping rules in case of DLT are presented in Section 6.6.1.1.

4.1.1.1.2. Dose Escalation Safety Review Period (Part A Only)

In Part A, the dose escalation safety review period is from the beginning of IV administration through Day 15 prior to initiating the GC.

Any AEs that meet the above criteria, but occur after the dose escalation safety review period of Part A may be considered by the DSMB in the evaluation for Part B dose selection. Further details are presented in Section 6.6.1.

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 has been evaluated by the DSMB and approved by the sponsor. Doses may be adjusted based on the PK and safety findings of the preceding dose group(s).

4.1.2. Part B: Phase 2, Double-Blind, Placebo-Controlled Study

Part B is a Phase 2, double-blind, PBO-controlled, parallel design study to characterize the biomarker response (plasma IL-2; primary endpoint) in peripheral blood following GC, Safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years of age inclusive) with histology-confirmed CeD will also be analyzed. 16 participants (approximately 4 participants per dose group) will be randomized 1:1:1:1 and stratified by participation in biopsy substudy to the following treatment groups:

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

Initiation of Part B will occur following the DSMB review of available safety and PK data from Part A and the sponsor's approval.

Part B comprises 4 periods and 1 sub-study:

- **Screening period:** ≤ 28 days
- **Run-in period:** 21 days
    - Eligible participants will undergo a 1-day 9g GC on first day of run-in period (21 days before administration of first dose of study drug) to confirm symptomatic response to oral GC (see Section 8.2.1).
    - Non-responders (participants with asymptomatic response to GC) will be screen-failed from the study.
    - Symptomatic responders eligible to participate in the study will be randomized and will proceed to the Treatment period.
- **Treatment period:** 7 days
    - Symptomatic responders to the run-in GC will be randomized 1:1:1:1 to one of the 4 Treatment groups and administered study intervention IV for 3 administrations (1 administration every 3 days starting at Day 1).

      Post infusion, participants will be monitored in the clinic for 4 hours for infusion-related reactions (see Appendix 9).

- **Observation/follow-up period:** 358 days
  - **Post-dosing GC on Day 15:** All participants will return to the clinic on Day 15 to receive a 1-day 9 g oral GC to assess plasma IL-2 biomarker response (primary endpoint) to gluten and collect symptom information.
  - **Post-dosing GC at Weeks 12, 24, and 36:** All participants will return to the clinic to receive a 1-day 9 g oral GC to assess plasma IL-2 biomarker response to gluten and collect symptom information (exploratory endpoints).
  - **Follow-up visits: on Day 28 and Week 52**.
- **Biopsy Substudy** (applicable sites only)
  - Approximately 50% of Part B cohort participants at applicable sites will receive biopsies (see Section 8.2.4) at screening and Week 52 per the SoA. Note: for participants in the biopsy sub-study the EGD with biopsy will be performed only once all eligibility criteria, except for Inclusion Criterion #5, are fulfilled.

Note: For Part B, DSMB will review data periodically and make recommendations to the sponsor to continue the study as planned, modify the study, temporarily suspend or terminate the study.

4.1.3. Part C: Phase 2, Double-Blind, Placebo-Controlled Study

Part C is a Phase 2, double-blind, PBO-controlled, parallel design study to compare the biomarker response (plasma IL-2; primary endpoint) following GC on Day 15. Safety, tolerability, and PK of KAN-101 in adult participants (18 to 70 years of age inclusive) with histology-confirmed CeD will be assessed. Approximately 104 participants (approximately 26 participants per dose group) will be randomized 1:1:1:1 and stratified by participation in biopsy substudy to the following treatment groups:

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

Initiation of Part C will occur following the DSMB review of available safety data from Part B and the sponsor's approval.

Additional safety data including orthostatic vital signs, temperature, RR and post-dose/GC safety labs will be collected in Part C as detailed below.

Part C comprises 3 periods and 1 sub-study:

- **Screening period:** Day -28 to Day -1
- **Treatment period:** Day 1 to Day 7
    - Participants will be randomized 1:1:1:1 to one of the 4 treatment groups and administered study intervention IV for 3 administrations (1 administration every 3 days starting at Day 1).
        - Orthostatic vital signs, temperature, and RR will be measured at times decribed in the SoA.

  Follow-up period: Day after last dose till Day 364 (±3 days). Participants will be followed for additional approximately 358 days which will include:

    - **Post-dosing GC on Day 15:** All participants will return to the clinic on Day 15 to receive a 1-day 9 g oral GC.
    - **Post-dosing GC at Weeks 12, 24, and 36:** All participants will return to the clinic to receive a 1-day 9 g oral GC.
    - **Safety follow-up visits on Day 28 and Week 52**: includes assessment of AEs, clinical signs and symptoms, and safety labs (Week 52 only).
- **Biopsy Substudy** (applicable sites only)
    - Approximately 50% of participants in Part C (at applicable sites) will receive biopsies (see Section 8.2.4) at screening and Week 52 per the SoA. Note: for participants in the biopsy sub-study the EGD with biopsy will be performed only once all eligibility criteria are fulfilled.

Note: For Part C, DSMB will review data periodically and make recommendations to the sponsor to continue the study as planned, modify the study, temporarily suspend or terminate the study.

4.2. Scientific Rationale for Study Design

In KAN-101-01 study, participants treated with 0.15 mg/kg, 0.3 mg/kg and 0.6 mg/kg of KAN-101 exhibited T-cell tolerance to gliadin by demonstrating minimal change or a decrease in the gliadin-specific T-cell response to GC compared to participants in the placebo

who exhibited an increase in the gliadin-specific T-cell response following GC. In addition, participants treated with 0.6 mg/kg KAN-101 exhibited lower median interleukin-2 (IL-2) levels after GC compared to the IL-2 levels in Placebo or 0.15 mg/kg and 0.3 mg/kg KAN-101 groups. Overall, KAN-101 demonstrated an acceptable safety and tolerability profile in both Part A and Part B of the study at all doses tested. There were no deaths, SAEs, Grade 3 TEAEs, or DLTs observed; therefore, no MTD was determined in this study. With expected efficacy dose of 1.2 mg/kg or over, higher doses may be explored in future studies. Further details are provided in the KAN-101 IB.

In KAN-101-01 and non-clinical models, T-cell tolerance induction was observed as early as 1 week after drug administration in celiac patients, supporting the timing of the primary endpoint assessment and the safety review period.

In the previous protocol for this study, 1.2 mg/kg, 3.0 mg/kg and 6.0 mg/kg KAN-101 were planned to be evaluated in a MAD 3+3 design (Part A). Based upon emerging data from Part A, the protocol has been amended to proceed to Part B following completion of Part A 3.0 mg/kg dose cohort. The decision not to test 6.0 mg/kg was not due to any safety concerns or exposures which exceeded the NOAEL. Part B evaluated 0.6 mg/kg, 1.2 mg/kg, and 3.0 mg/kg in a dose-ranging design (Part B) in CeD participants on GFD

Sixteen participants were randomized at which time, study was paused and ad-hoc DSMB was convened to assess emerging safety data.

After review of emerging data by DSMB, Part B was closed due to concerns for sensitization by screening GC, potentially leading to higher frequency and severity of AEs observed after dosing with KAN-101/PBO. The study remains blinded.

In amendment 3 of this protocol, Part C is added. In Part C, the screening GC requirement is removed. As a result, the primary objective will now be evaluating the change in magnitude of IL-2 response before and after GC in KAN-101 treated versus placebo participants on Day 15. Furthermore, in order to get more insight into the events immediately subsequent to dosing, additional assessments including orthostatic vital signs, temperature, and RR are collected. Additionally, safety labs (hematology and chemistry) will be collected in case of orthostatic hypotension, syncope, or TEAE, Grade 3 or greater.

4.2.1. Choice of Contraception/Barrier Requirements

KAN-101 has not been evaluated in EFD study. The effects of KAN-101 on conception, pregnancy, and lactation are unknown. Therefore, the use of a highly effective contraception and a barrier method is required for WOCBP, and all men who are not sterile (biologically or surgically) must commit to the use of 1 reliable method of birth control for at least 21 days after the last dose of study intervention (see Appendix 4 for further information).

The observed $t_{1/2}$ of KAN-101 from the FIH study ranges between 3.74 to 36.8 minutes across 0.15 mg/kg to 1.2 mg/kg doses with no accumulation observed for repeat dosing. Pre-clinical toxicology and clinical information for KAN-101 are summarized in the IB.

4.3. Justification for Dose

4.3.1. Exposure Limits for Dose Escalation

The measurement of KAN-101 exposure levels in GLP toxicology studies was impacted by sample processing of the serum samples and therefore is not being used to calculate the exposure and safety margins. To calculate the KAN-101 exposures and safety margins, the KAN0009 peptide, a component of KAN-101, was measured in GLP toxicology studies and converted to KAN-101 exposure using a factor that was empirically determined during assay development.

In this study, the KAN-101 C_{max} and AUC_{last} exposure limits for dose escalation are determined to be 346,969 ng/mL and 202,646 ng.hr/mL, respectively, based on the NOAEL (74 mg/kg) exposures in the cynomolgus monkey study.

4.3.2. Dose Justification for Part A and Part B and Part C

Based on KAN-101-01 study results, doses covering projected efficacious doses (0.6 mg/kg and over) will be evaluated in this Phase 1b open-label /Phase 2 double-blind placebo-controlled study for pharmacodynamic activity, safety, and tolerability of KAN-101 in participants with celiac disease.

The proposed doses for Part A are 1.2 mg/kg, 3 mg/kg and 6 mg/kg administered in 3 doses 3 days apart. Based upon emerging data from Part A, the protocol has been amended to proceed to Part B following completion of Part A 3.0 mg/kg dose cohort. The decision not to test 6.0 mg/kg was not due to any safety concerns or exposures which exceeded the NOAEL. Single doses of 1.2 mg/kg tested in KAN-101-01 study were well-tolerated. Given the short $t_{1/2}$ of KAN-101, minimal accumulation is expected after repeat dosing with similar safety and tolerability as single doses thus providing a bridge for a safe and tolerable starting dose proposed for this study.

Table 1 presents the predicted exposures and safety margins relative to the NOAEL exposures for the proposed doses in Part A. The predictions presented linearly extrapolate the exposures observed at 1.2 mg/kg in KAN-101-01 study.

Table 1. Projected Exposures and Safety Margins Following Repeat IV Doses of KAN-101

Dose[a] (mg/kg)	C_{max}[b] (ng/mL)	AUC_{last}[b] (ng.hr/mL)	SM_C_{max}[c] (fold)	SM_AUC_{last}[c] (fold)
1.2	19,470	13,920	17.8	14.6
3	48,675	34,800	7.1	5.8

a. Represents a dosing frequency of every 3 days for 3 doses.
b. C_{max}, and AUC_{last} values after the third IV dose are presented in the table.
c. SM is calculated relative the cynomolgus monkey NOAEL exposures (C_{max}= 346,969 ng/mL and AUC_{last}= 202,646 ng.hr/mL)

The predicted KAN-101 C_{max} and AUC_{last} at starting dose of KAN-101 1.2 mg/kg are approximately 17.8 and 14.6 fold below the pre-defined exposure limits (Table 1).The

highest proposed dose in Part A of 6 mg/kg IV Q3 days is estimated to provide an exposure margin of 3.6- and 2.9-fold for C_{max} and AUC_{last}, respectively.

This frequency of dosing in the study is supported by the nonclinical experimental EAE mouse model that demonstrated that dosing every 3 days was more effective than weekly dosing as well as by the clinical efficacy biomarker data from the FIH study.

In Part B and Part C, KAN-101 will be be tested at 3 dose levels of 0.6 mg/kg, 1.2 mg/kg and 3.0 mg/kg or placebo administered in 3 doses 3 days apart.

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

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

For Part A and Part C: All inclusion/exclusion criteria must be met and confirmed prior to randomization.

For Part B: all inclusion criteria (Section 5.1), except Inclusion Criterion #5, and all exclusion criteria (Section 5.2) must be met and confirmed prior to entry into the run-in period and run-in GC assessment at Day -21. All inclusion/exclusion criteria must be met and confirmed prior to randomization.

For Part B Biopsy Substudy: all inclusion criteria (Section 5.1), except Inclusion Criterion #5, and all exclusion criteria (Section 5.2) must be met and confirmed prior to

undergoing the screening biopsy. All inclusion/exclusion criteria must be met and confirmed prior to randomization.

For Part C Biopsy Substudy: all inclusion criteria (Section 5.1), and all exclusion criteria (Section 5.2) must be met and confirmed prior to undergoing the screening biopsy. All inclusion/exclusion criteria must be met and confirmed prior to randomization.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Participants aged 18 years to 70 inclusive (or the minimum age of consent in accordance with local regulations) at screening.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Disease Characteristics:

2. Previous diagnosis of CeD, based on documentation in the source data:

    - Positive celiac serology (eg, tissue transglutaminase IgA antibody and/or deamidated DGP IgG)

        AND

    - Intestinal histology consistent with ≥ Marsh Type 2 (Section 10.11) or with evidence of villous atrophy.

3. Have HLA-DQ2.5 genotype (HLA-DQA1*05 and HLA-DQB1*02 (homozygotes or heterozygotes)).

4. Negative or weak positive for transglutaminase IgA AND negative or weak positive for DGP-IgA/IgG during screening.

    - For tTG, a result of ≤10 U/mL will be considered negative or weak positive.

    - For DGP, a result of <30 U/mL will be considered negative or weak positive.

5. **Part B ONLY (prior to randomization):** Demonstrates a symptomatic response following a 1-day oral GC performed during Run-in, defined as having at least 1 moderate to severe GI symptom (either diarrhea, abdominal pain, bloating, or nausea) the day of the GC.

    - Refer to Section 8.2.1.1 for symptomatic response criteria.

Other Inclusion Criteria:

6. Have followed a gluten-free diet for ≥12 months immediately prior to study entry (self-reported).

7. Capable of understanding the ICD, complying with protocol requirements, and has signed the ICD.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Refractory CeD, defined as severe persistent or recurrent malabsorptive signs or symptoms with substantial villous atrophy (ex. documented Marsh score 3c in source data) despite strict adherence to a GFD for at least 12 months in the absence of other disorders.

2. Selective IgA deficiency.

3. Positive for HLA-DQ8 (*DQA1*03, DQB1*0302*).

4. Known wheat allergy.

5. Known history of severe hypersensitivity reactions or anaphylaxis to gluten.

6. Previous oral GC within 12 months.

7. History of dermatitis herpetiformis.

8. Active gastrointestinal disease (eg, inflammatory bowel disease, any forms of colitis, uncontrolled IBS, peptic ulcer disease, eosinophilic esophagitis, and active GI infections).

9. Diagnosis of Type-I diabetes.

10. Clinical signs and symptoms consistent with COVID-19 or confirmed infection by appropriate laboratory test within the 2 weeks prior to screening or dosing.

    - *Note:* participants who experienced symptoms consistent with COVID-19 or confirmed infection during the screening period may be rescreened after 4 weeks.

11. Prior severe course of COVID-19 requiring extracorporeal membrane oxygenation or mechanical ventilation within the last 12 months.

12. Other uncontrolled or significant medical (including active infections) or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

13. Previous treatment with tolerance-inducing therapies for CeD.

14. Current use of any prohibited concomitant medication(s) or participants unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

15. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

16. Renal impairment as defined by an eGFR in adults of <60 mL/min/1.73m^2. Based upon participant age at screening, eGFR is calculated using the recommended formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

17. Hepatic dysfunction defined as:

    - Total bilirubin ≥1.5 × ULN (except for Gilbert's syndrome)
    - AST ≥1.5 × ULN
    - ALT ≥1.5 × ULN
    - Alkaline phosphatase > 1.5 × ULN

18. Hematologic abnormalities defined as:

    - ANC ≤1000 mm^3
    - Platelets ≤100 × 10^9/L
    - Hemoglobin ≤10 g/dL
    - WBC outside the normal range and assessed as clinically significant by the investigator.

19. Positive for HIV, hepatitis B, and/or hepatitis C.

    - For Hepatitis B, all participants will undergo testing for HBsAg and HBcAb during screening. Participants who are HBsAg positive are not eligible for the study. Participants who are HBsAg negative and HBcAb positive will be reflex tested for HBsAb and HBV DNA. If HBsAb is positive and HBV DNA negative, they may be enrolled in the study; if HBsAb is negative and/or HBV DNA is positive, the participant is not eligible for the study.

    - For Hepatitis C, all participants will undergo HCVAb during screening. Participants with positive HCVAb tests will be reflex tested for HCV RNA. Only participants with negative HCVAb or HCV RNA will be allowed to enroll.

    - For HIV, known history of HIV based on documented history with positive serological test, or positive HIV serologic test at screening, tested at central lab.

20. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias).

    - If the baseline uncorrected QT interval is >450 ms, this interval should be rate corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting.

    - If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility.

    - Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

Other Exclusion Criteria:

21. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

Following a GFD for at least 12 months is required for study entry (see Section 5.1).

Participants are required to continue to follow a GFD during the study; incidental gluten exposure will be collected daily as part of an eDiary and reviewed at every study visit (see Section 8.3.1).

Participant's use of herbal medicines and probiotics should be reported on the CRF and should remain stable during the study.

5.3.3. Caffeine, Alcohol, and Tobacco

Participants should avoid excessive consumption of alcohol prior to visits with safety lab assessments as specified in the SoA.

5.3.4. Activity

Participants should avoid strenuous physical activities prior to visits with safety lab assessments as specified in the SoA.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. For participants who are screen failed (prior to the run-in GC, Part B only), a minimal set of screen failure information, including demography, screen failure details, eligibility criteria, and any AE or SAE, are required to be collected on the CRF. Screen failure data for participants who are failed (after the run-in GC,

Part B only) will be reported on the CRF. CRF reported data will include, but is not limited to, demographics, medical/CeD history, and prior CeD treatments. Participants who screen-fail (after the run-in GC, Part B only) will also have non-CRF-reported data collected, including, but, not limited to, HLA, CeD serology, biopsy results, CDSD v2.1 data collected up to date of screen failure, and GC IL-2 biomarker data. Non-CRF reported data will be transferred to the sponsor, or sponsor's designee (Pfizer).

Individuals who do not meet the criteria (prior to run-in GC, Part B only) for participation in this study (screen failure) may be rescreened.

Individuals in Part A and Part C who do not meet the criteria for participation in this study (screen failure) may be rescreened *EXCEPT* as noted below.

Repeating HLA genotyping is not needed during rescreening period. Repeating celiac serology and/or EGD with biopsy (for participants in the biopsy substudy) is not required during rescreening if it is within 3 months of the initial assessments during the first screening period.

Participants **cannot be rescreened** if they fail screening due to:

- HLA genotyping assessment at screening.
- Positive for HIV, HBV, or HCV.

For Part B only:

- Individuals who complete the run-in GC, are symptomatic, but are not randomized are eligible for re-screening after 12 months have elapsed.
- Participants **cannot be rescreened** if they fail screening due to:
  - Reasons listed above.
  - Asymptomatic response to the run-in gluten challenge (Section 8.2.1.1).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products/auxiliary medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to KAN-101 or PBO for KAN-101.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	KAN-101	PBO
Arm Name (group of participants receiving a specific treatment or no treatment)	**Part A:** Cohort 1 and 2 **Part B:** Group 2, 3, and 4 **Part C:** Group 2, 3, and 4	**Part A:** N/A **Part B:** Group 1 **Part C:** Group 1
Type	Drug	PBO
Dose Formulation	Solution in a single-use glass vial for dilution into saline bag for IV infusion	Solution for infusion in a saline bag
Unit Dose Strength(s)	CCI [redacted]	N/A
Dosage Level(s)	CCI [redacted]	PBO
Route of Administration	IV	IV
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	Placebo
Sourcing	Provided centrally by the sponsor. Further details are presented in the IPM.	Provided locally by the site. Further details are presented in the IPM.
Packaging and Labeling	Study intervention will be provided in glass vials. Each vial will be labeled as required per country requirement. In Part B and Part C, study intervention will be blinded once diluted in a saline bag.	Study intervention will be provided in saline bags. Each saline bag will be labeled as required per country requirement. In Part B and Part C, study intervention will be blinded.

Study Arm(s)				
Part A (open-label)				
Arm Title	Cohort 1		Cohort 2	
Arm Type	Experimental		Experimental	
Arm Description	Participants will receive 1.2 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.		Participants will receive 3.0 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.	
Associated Intervention Labels	KAN-101		KAN-101	
Part B and Part C (double-blind)				
Arm Title	Group 1	Group 2	Group 3	Group 4
Arm Type	Placebo	Experimental	Experimental	Experimental
Arm Description	Participants will receive PBO IV every 3 days starting on Day 1 and ending on Day 7.	Participants will receive 0.6 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.	Participants will receive 1.2 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.	Participants will receive 3.0 mg/kg IV every 3 days starting on Day 1 and ending on Day 7.
Associated Intervention Labels	PBO	KAN-101	KAN-101	KAN-101

6.1.1. Administration

Administration of KAN-101 will be by IV infusion over approximately 30 minutes for the following dosages: 0.6 mg/kg, 1.2 mg/kg, or 3.0 mg/kg mixed with saline to have the final 250 mL IV infusion solution.

PBO will be 250 mL normal saline only. Administration of PBO will be by IV infusion over approximately 30 minutes.

In Part B and Part C only, for participants who may have experienced adverse events following previous study intervention administration, prophylactic medication such as ondansetron may be administered 30 minutes before subsequent study intervention administration at the discretion of the investigator.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM or other specified location.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM for storage conditions of the study intervention once diluted.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify Pfizer within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (ex. study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Part A is an open-label study. The investigator's knowledge of the treatment assignment must not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. Potential bias will be reduced by the following steps: central randomization and DSMB review.

Study intervention will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

This is a 3 part study; Part A is open-label and Part B and Part C are double-blinded .

6.4.1. Blinding of Participants

- **Part A** is open-label.
- **In Part B and Part C**, participants and their caregivers will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

- **Part A** is open-label.
- **In Part B and Part C**, investigators and other site staff will be blinded to participants' assigned study intervention. Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

Unblinded personnel include site staff involved in study intervention preparation and allocation (eg, data systems support and pharmacists).

6.4.3. Blinding of the Sponsor

- **Part A** is open-label. The data for dose escalation in Part A will be presented and reviewed by the DSMB in an open-label, unblinded manner.

- **For Part B and Part C**, sponsor staff will be blinded to participants' assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention. Sponsor staff who are not directly involved with the conduct of this study will prepare analyses and documentation containing unblinded data while the study is ongoing to support interactions with the DSMB.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, Pfizer must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study--specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose.

Compliance with the study intervention is defined as receiving 100% of the doses as specified per protocol.

6.6. Dose Modification

In Part B and Part C, no dose modification is allowed following selection of doses based on safety and tolerability of doses studied in Part A.

In Part A, the decision to proceed to the next dose level of KAN-101 (either an increase or a decrease) will be made by the study team and DSMB during the dose escalation safety period (see Section 6.6.1).

Details of the DSMB are presented in Section 10.1.5.

If the decision is made to dose escalate, it is the sponsor's discretion whether to proceed with escalation, expand the same dose cohort, or to modify doses based on emerging data.

6.6.1. Dose Escalation Safety Review Period for Part A

In Part A, the dose escalation safety review period is from the beginning of IV administration through Day 15 prior to GC. Any AEs that meet DLT criteria (Section 4.1.1.1.1) but occur after the dose escalation safety monitoring period of Part A may be considered by the DSMB/Sponsor in the evaluation of Part A dose escalation and Part B dose selection.

The length of monitoring periods for safety review is supported by nonclinical exposure data and FIH clinical data, suggesting KAN-101 will have cleared 5 half-lives, and clinical data demonstrating that the tolerance induction mechanism can develop within 1 week of dosing. Participants will be monitored in the clinic for 4 hours following the IV administration of study intervention.

AEs and any abnormal clinical parameters, including laboratory findings and available PK data, observed during this period will be used by the DSMB to determine whether dose escalation should proceed. DSMB review of ongoing safety data will continue after dose escalation has either been completed or stopped and participants remain active in the study.

Dose escalation in Part A can proceed after the following criteria are met:

- All 3 participants have been dosed.
- DSMB, sponsor medical monitor and investigators who enrolled participants have reviewed all available safety data for dosed subjects, including:
    - A minimum of 1 week safety and tolerability data after the last study intervention dose;

      AND

    - All available PK data after the last study intervention dose.

6.6.1.1. Individual and Cohort Stopping Rules

Dose escalation stopping rules will be used to determine whether the MTD has been attained. Dose escalation will be stopped if it is determined that the limits of safety and/or tolerability have been reached based on the criteria described in this section. This decision will be made after a discussion takes place between the DSMB, the sponsor study team and the investigator. The sponsor study team may not overrule the DSMB or investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention. If any dose cohort is repeated, this additional cohort will be considered a separate cohort for the purpose of these dose escalation stopping rules.

For DLT definition for Part A and further details, see Section 4.1.1.1.1.

At any time:

- Any TEAE at Grade 3 or higher experienced during the study will be reviewed by DSMB.

- Any ≥ Grade 4 AE will result in notification of the FDA in parallel with DSMB and study dosing and enrollment will be paused pending review by FDA.
    - The study would only continue after consultation with the FDA.
- No participant with a DLT will be replaced.

In Part A:

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

In Part B and Part C:

- DSMB will review unblinded available clinical, laboratory and PK data (if available) periodically or if there is a Grade 3 or above, related AE during treatment period and will make recommendations for study continuation as defined in the DSMB charter.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of study intervention greater than the maximum dose of study intervention according to the protocol within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to the sponsor **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis as soon as overdose is identified but no later than 24 hours from the last over-dosed study intervention if requested by the study medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

All participants are required to maintain stable dosing of permitted prescribed and OTC medications for the duration of the study.

6.9.1. Prohibited During the Study

The following therapies are prohibited during the study:

- Any additional therapies to treat CeD.
- Other investigational agents, including biologic or non-biologic immunosuppressive or immunomodulatory therapies.
- Non-investigational systemic immunosuppressive and immunomodulatory therapies (eg, systemic corticosteroids).
- All vaccines between 4 weeks prior to dosing through 4 weeks from the last dose of study intervention; vaccines are permitted at all other times during the study.

6.9.2. Permitted During the Study

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

HRT use by postmenopausal women is permitted if they meet requirements in Appendix 4.

Any other medication that is considered necessary for the participant's welfare that is not expected to interfere with the evaluation of KAN-101 may be given at the discretion of the investigator and documented on the CRF.

In cases involving concomitant therapies whose predicted interference with KAN-101 is unknown to the investigator, the sponsor should be contacted for discussion.

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 CRF. Participants should report any changes to permitted medications during the study to the investigator as soon as they occur. Medication changes must be documented in the participant's record and CRF.

Patients being treated for IBS symptomology will be allowed to continue therapy (eg, dicyclomine) unless the drug is specifically prohibited.

Antidiarrheal (eg loperamide) or antiemetics (eg metoclopramide or ondansetron) may be used for IBS symptomatic treatment if warranted by symptomology unless the drug is specifically prohibited. If given at a study visit, use must be recorded on the CRF.

6.9.3. Rescue Medicine

There is no rescue therapy to reverse AEs observed with KAN-101; standard medical supportive care, (such as ondansetron) may be provided to manage AEs.

Medication such as Ondansetron is:

Part A: allowed in as symptomatic treatment,

Part B and Part C: allowed as symptomatic treatment of an AE after study drug intervention; and optionally allowed as pre-treatment to subsequent study intervention administration at investigator discretion based on the occurrence of AEs after previous study drug administration.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- An AE that requires permanent discontinuation of study treatment*;
- Noncompliance with the protocol;
- Investigator decision;
- Participant becomes pregnant;
- Participant death;
- Participant lost to follow-up;
- Termination of the study by the sponsor;

- Voluntary withdrawal of consent by the participant.

* Note: AEs leading to the discontinuation of study intervention will be followed until resolution, resolution to baseline, or the event is considered stable or chronic.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

Participants who withdraw from treatment and do not receive 3 full doses should not receive the GC or have plasma samples taken for IL-2 on GC days.

7.1.1. Liver Injury

A participant who meets the criteria as described in Appendix 6 will be withdrawn from study intervention.

7.1.2. Pregnancy

Pregnancy tests are conducted as specified per the SoA and administration of study intervention or GC will occur only in the presence of a negative pregnancy test.

If a participant is confirmed to be pregnant (see Section 8.3.6) during any visit, conducting of GCs and further dosing with study intervention will be discontinued immediately and permanently.

Section 8.4.5.1 describes the follow-up activities if a participant meets EDP criteria.

7.1.3. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.1.4. Temporary Discontinuation

In cases where a temporary discontinuation or dosing interruption is required, the total infusion should be completed within 6 hours of thawing the drug product. Any temporary discontinuations or interruptions of study intervention should be documented in the CRF.

See Appendix 9 for detailed guidance regarding infusion administration interruptions due to IRR.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Investigator's decision;
- Participant death;
- Participant lost to follow-up;
- Termination of the study by Sponsor;
- Voluntary withdrawal of consent of participant.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol -specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol -required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol -required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 225 mL in Part A, 150 mL in Part B, and 190 mL in Part C. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by the sponsor, provided the total volume taken during the study does not exceed 550 mL during the study.

8.2. Efficacy Assessments

Efficacy assessments are not performed. PD activity is being measured at times specified in the SoA.

8.2.1. Gluten Challenge

Participants are required to fast for at least 8 hours, except for water and any medications they might have previously been prescribed, prior to the study visits where GC are performed (see SoA).

- **Part A:** All eligible, enrolled participants will undergo GC at Day 15.
- **Part B:** All eligible, enrolled participants will undergo 1-day GC during run-in and at times as specified in the SoA.
- **Part C:** All eligible, enrolled participants will undergo 1-day GC at times as specified in the SoA.

In Part B, during run-in period: all participants must meet all inclusion criteria before commencement of GC except Inclusion Criterion #5.

A qualified staff member will prepare the GC in bottles at times specified in the SoA.

Participants will consume 9g of gluten protein PO in the clinic and avoid foods (only water is permitted) at least 30 minutes after completion of the gluten drink. The participant will be observed for at least 4 hours to monitor for hyperacute reactions requiring medical treatment and collection of biomarker samples.

Compliance with the GC is defined as completion of the entirety of the 9g GC, including container wash steps, within approximately 15 minutes. Participants will consume the GC on site under the observation of site staff.

Any symptoms associated with the GC should be recorded as AEs (See Section 8.4). Any AEs associated with the GC study assessment are separate to AEs related to study intervention (KAN-101/PBO).

8.2.1.1. Confirmation of Symptomatic Response to Run-in GC (Part B Only)

For Inclusion Criterion # 5:

- Symptomatic response to the run-in GC is defined as at least 1 moderate to severe GI symptom (either diarrhea, abdominal pain, bloating, or nausea) on the day of the GC.

  Either/or

- Symptom severity will be assessed using CDSD v2.1 scores on the day of the GC (see Section 8.2.3.1).

8.2.2. Plasma IL-2 Biomarker Assessment

Plasma samples will be collected to assess the magnitude of biomarker response of IL-2 pre- and post-GC in peripheral blood (Part A – exploratory endpoint; Part B and Part C – primary endpoint on Day 15 and secondary endpoints on Weeks 12, 24, and 36).

Further details are presented in Section 8.7.

8.2.3. Patient Reported Outcomes

8.2.3.1. CDSD v2.1

The CDSD v2.1, a novel patient-reported outcome measure developed for use with patients with CeD, consists of five symptoms including diarrhea, abdominal pain, bloating, nausea, and tiredness. The CDSD v2.1 assesses severity, in five scales from “none” to “very severe”, and frequency. The CDSD v2.1 will be assessed daily as part of the eDiary beginning during the screening period after signing the ICD.

The CDSD v2.1 should be completed for at least a minimum of 7 consecutive days during screening at any time prior to the baseline visit (Day 1) in Part A and Part C and prior to run-in GC visit (Day -21) for Part B. After screening and through the end of the study, compliance with the CDSD v2.1 is defined as 80% completion.

8.2.3.2. PGIC

The PGIC is a patient-completed question to assess the overall impression of disease improvement experienced by the patient. The PGIC score ranges from “much better” to “much worse”. The PGIC will be assessed at visits specified in SoA.

8.2.3.3. PGIS

The PGIS is a patient-completed question to assess the overall impression of disease severity experienced by the patient. The PGIS score ranges from “None” to “Very Severe”. The PGIS will be assessed at visits specified in SoA.

8.2.4. Esophagogastroduodenoscopy With Biopsy (Biopsy Substudy Only)

As part of the biopsy substudy in Part B and Part C, EGD with biopsies will be collected from participants at applicable sites at times specified in the SoA.

Urine pregnancy test may be performed prior to EGDC per local practice guidelines. EGD with biopsy will be performed by a qualified gastroenterologist at each site. All study gastroenterologists will be trained on the study-specific procedures for obtaining the biopsy, including the location and number of biopsies to be obtained, and procedures for storing and shipping of samples.

Approximately 6 duodenal biopsies will be obtained.

Endoscopy data obtained previously during screening up to 3 months prior to rescreening may be used as the baseline histology in a subject who has continued GFD and has not undergone a GC.

8.2.4.1. Histological Assessments (Biopsy Substudy only)

Tissue samples collected during biopsy as specified in the SoA will be analyzed for histological state (including, but not limited to: villus height, crypt depth, Marsh score, and IEL count) (see Appendix 10). Histology will be centrally read by qualified raters.

Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

Histology from EGD biopsy will be reviewed by a central review facility. The purpose of this review is to evaluate histology for celiac disease. Central histological review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the PI. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician--participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all histology as per site protocols.

8.3. Safety Assessments

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

All participants will be monitored continuously for AEs from screening until the safety follow-up visit on Week 52. AE severity will be assessed using the NCI CTCAE v5.0 or higher (see Appendix 10). The DSMB will review all SAEs and ≥ Grade 3 AEs that are assessed to be related to study drug as these events may occur. Any Grade 4 AEs assessed as related to study drug will result in notification of the FDA in parallel with the DSMB.

Participants will be monitored in the clinic for 4 hours following IV study drug administration for IRR (see Appendix 9).

For Part A, the DSMB will review cumulative safety data by dose cohort before opening a higher dose cohort. DLTs are defined in Section 4.1.1.1.1. Any DLT experienced during the Treatment period (Day 1 to Day 7) through Day 15 prior to GC will result in a pause in the study enrollment and a review of all available safety data by the DSMB prior to dosing any additional participants; further details for cohort stopping rules are presented in Section 6.6.1.1.

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

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Incidental Gluten Exposure Assessment

Incidental gluten exposure will be assessed daily as part of the participant's eDiary. Assessment of any incidental gluten exposure will be reviewed at all study visits.

8.3.2. Vital Signs

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

Vital signs will be monitored during and after study intervention infusions to assess for IRR (see Appendix 9). Vital signs will be taken before collection of laboratory tests. Height and weight will also be measured and recorded at screening only and captured on the CRF.

BP and PR assessment consists of a single measure of BP and a single PR. Sitting BP and PR measurement will be assessed with a completely automated device.

Manual techniques will be used only if an automated device is not available. BP and PR measurement should be preceded by at least 5 minutes of rest with the participant in a sitting position, in a quiet setting without distractions.

In amendment 3, Part C orthostatic vital signs including SBP, DBP, and PR will be collected as follows:

- Approximately 5 minutes pre-dose;
- Approximately 45 minutes, 2 hours, and then, every 2 hours until discharge, post dose.

Additionally, if a participant experiences treatment-emergent clinically significant orthostatic hypotension or syncope, then, in addition to supportive care, orthostatic vital signs including

DBP, SBP, and PR will be collected every 2 hours, until discharge. **Note**: if planned assessments (pre-dose and 45 min, 2 hr and 4 hour post-dose) overlap unplanned assessments, orthostatic vital signs will be measured only once, not twice at that time.

Measurement of orthostatic vital signs (SBP, DBP, and PR) will occur after:

1. participant has rested in supine position for 5 minutes
2. participant is in standing position for 1 min
3. Participant is in standing position for 3 minutes

Note: Clinically significant orthostatic hypotension (OH) is defined by a fall in systolic blood pressure over 20 mmHg or a fall of in diastolic pressure over 10 mm Hg within 3 minutes of standing. An increase in heart rate of over 30 bpm suggests postural tachycardia syndrome.(Freeman et al, 2011) In case of above, a Grade 3 AE will be documented.

8.3.2.1. Oral Temperature and Respiratory Rate

For Parts A and B, oral temperature and respiratory rate will be assessed. Temperature and respiratory rate findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted.

For Part C, oral temperature and RR will be assessed and recorded in clinical database at timepoints described in the SoA, ie,

- Approximately 5 minutes pre-dose;
- Approximately 45 minutes, 2 hours, and then, every 2 hours until discharge from the unit post dose.

Additionally, if a participant experiences treatment-emergent, clinically significant orthostatic hypotension or syncope, then, in addition to supportive care, temperature and RR will be collected every 2 hours, until discharge. **Note**: if planned assessments (pre-dose and 45 min, 2 hr and 4 hour post-dose) overlap unplanned assessments, temperature and RR will be measured only once, not twice at that time.

8.3.3. Electrocardiograms

A standard 12-lead ECG utilizing limb leads (with a 10-second rhythm strip) should be collected at screening using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. The ECG should be performed prior to blood draws and after the participant has rested quietly for at least 5 minutes in a supine position. When collected, ECG values should be entered in clinical database.

Unscheduled ECGs are permitted per the investigator's discretion.
In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

Fasting at least 8 hours is required for the clinical safety laboratory tests. See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol required- laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with any underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within the follow-up period after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

As part of amendment 3, if a participant experiences treatment-emergent, clinically significant orthostatic hypotension, syncope or treatment-related TEAE Grade 3 or above, then, in addition to supportive care, additional samples for safety laboratory tests (hematology, blood chemistry) will be collected.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.4.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations will be conducted at a central laboratory.

Non-protocol-specified laboratory evaluations as ordered by the investigator may be conducted at a local laboratory.

8.3.5. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded at screening only.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by the sponsor to obtain specific follow -up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention, through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically significant AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and the sponsor concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer Safety using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to the Sponsor

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to the sponsor on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to Pfizer Safety within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to Pfizer Safety of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country--specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention during the mandatory contraception period (see Appendix 4).
- A male participant who is receiving or has discontinued study intervention inseminates a female partner during the mandatory contraception period (see Appendix 4).
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP if they occur within 21 days after exposure:
- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
- A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 12 weeks after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial-EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to the sponsor as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow--up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver

to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention during the mandatory contraception period (see Appendix 4).
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure) within the last 21 days. An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease -Related Events and/or Disease -Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

Not applicable. The primary objective of the study is to evaluate PD activity following treatment with multiple doses of KAN-101 versus PBO.

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- Administration of a quantity of study intervention per administration or cumulative, which is above the maximum dose according to the protocol.
- Unintentional error in dispensing or administration of study intervention not in accordance with the protocol.
- Off-label use where study intervention is used for medicinal purpose not in accordance with the protocol.
- Intentional and inappropriate misuse of study intervention not in accordance with the protocol.
- Persistent or sporadic, intentional excessive use of study intervention, which is accompanied by harmful physical or psychological effects.
- Exposure to study intervention because of one's professional or non-professional occupation.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

In the event of a medication dosing error, Pfizer should be notified within 24 hours.

Medication errors should be reported to Pfizer within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of KAN-101 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Samples collected for measurement of plasma concentrations of study intervention will be analyzed using a validated analytical method in compliance with applicable SOPs.

The actual times for PK assessment may change, and if needed, additional PK samples may be taken at times specified by Sponsor, provided the total blood volume taken during the study does not exceed 550 mL during any period of 56 consecutive days. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within 2 minutes for samples that are planned at less than 1 hour, and within 5 minutes for samples planned between 1-7 hours after dose administration of the nominal time respectively relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT.

Samples will be used to evaluate the PK of KAN-101. Samples collected for analyses of KAN-101 plasma concentration may also be used to evaluate safety or PD aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes, and not reported in the CSR.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to Pfizer. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Genetic analyses will not be performed on these whole blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

8.6.1. Specified Genetics

To determine study eligibility, all participants will be assessed via central laboratory for HLA-DQ2.5 genotype (see Inclusion Criteria, Section 5.1) and absence of HLA-DQ8 genotype (see Exclusion Criteria, Section 5.2).

Details on processes for collection and shipment of these samples can be found in the study laboratory manual.

8.7. Biomarkers

Collection of samples for biomarker research is also part of this study.

In Part A, the following samples for biomarker research are required and will be collected from all participants in the study at times specified in the SoA:

- Plasma (plasma IL-2 biomarker assessment; see Section 8.2.2).
- PBMC for future exploratory use.

In Part B, the following samples for biomarker research are required and will be collected from all participants in the study at times specified in the SoA:

- Plasma for IL-2 (plasma IL-2 biomarker efficacy assessment; see Section 8.2.2)

In Part C, the following samples are required and will be collected from all participants as listed below:

- Plasma for IL-2 for PD activity on Day 15, Weeks 12, 24, and 36 approximately 5 minutes pre-GC and 4 hours (±15 minutes) post-completion of GC;
- Plasma for other biomarkers on Days 1, 4, and 7 approximately 5 minutes pre-dose and 4 hours (±15 minutes) post-end-of-infusion.

  Note: In addition to planned plasma sample collection described above, if a participant experiences clinically significant orthostatic hypotension, syncope or a treatment-related TEAE Grade 3 or above, then, in addition to supportive care, additional plasma samples may be collected on Day 1, 4, or 7 for biomarkers.

Details on processes for collection and shipment of these samples can be found in the study laboratory manual.

8.7.1. Residual Research Samples

Any remaining residual samples not used for protocol-specified assessments will be retained as local regulations and IRB/ECs allow.

- Samples include, but are not limited to:
    - Plasma
    - PBMC for biomarker assessments (Part A only)
    - Histopathology samples

Residual research samples may be used for research related to the study intervention(s) or celiac disease. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the residual samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the study laboratory manual.

8.8. Immunogenicity Assessments

Blood samples will be collected for determination of ADA as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of ADA may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

Genetic analyses will not be performed on these whole blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to Pfizer. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Immunogenicity information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.9. Health Economics

Health economics will not be assessed in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

9.1.1. Estimands

9.1.1.1. Part B

Estimand 1 will be used for Part B primary endpoint:

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

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

9.1.1.2. Part C

Estimand 2 will be used for the primary endpoint main analysis in Part C.

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

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

9.1.2. Multiplicity Adjustment

There is no multiplicity adjustment. All hypothesis testings will be performed at a nominal significance level of 0.05 (2-sided).

9.2. Analysis Sets

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

Participant Analysis Set	Description
Part A	
Enrolled	All participants who sign the ICD and are assigned to study intervention in Part A.
Full analysis set	All participants who receive any portion of study intervention in Part A.
Safety analysis set	All participants who receive any portion of study intervention in Part A. It is the same as FAS.
PK analysis set	All participants who apply any portion of study intervention and have at least 1 concentration value in Part A.
Part B	
Enrolled	All participants who sign the ICD.
Full analysis set	All participants who are randomly assigned to study intervention and receive any portion of study intervention in Part B. Participants will be analyzed according to the intervention they are randomized.

Participant Analysis Set	Description
Safety analysis set	All participants who receive any portion of study intervention in Part B. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All participants who receive any portion of study intervention and have at least one concentration value in Part B.
Part C	
Enrolled	All participants who sign the ICD.
Full analysis set	All participants who are randomly assigned to study intervention and receive any portion of study intervention in Part C. Participants will be analyzed according to the intervention they are randomized.
Safety analysis set	All participants who receive any portion of study intervention in Part C. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All participants who receive any portion of study intervention and have at least one concentration value in Part C.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

Descriptive statistics will be used in general to summarize study results, ie, count and percent will be presented for binary endpoints and categorical endpoints; statistics for continuous variables will include number of observations, mean, standard deviation, minimum, 1st, 2nd, 3rd quartiles, and maximum. The coefficient of variation and geometric mean will also be included, where appropriate. Graphics may be used to present the data.

A review will be conducted at the end of Part A to assess for preliminary safety and PK to confirm dose selection for Part B and Part C. This review will be exploratory in nature, so no formal statistical testing is planned; all analyses of Part A data will be descriptive only.

9.3.1.1. Analyses for Continuous Endpoints

For continuous endpoints in Part C, the change from baseline will be analyzed by timepoint using ANCOVA model with treatment as the factor, baseline as a covariate. Endpoints without baseline will be analyzed by ANOVA with treatment as the factor. Comparison of

KAN-101 to PBO (providing LSM of the treatments, LSM of the treatment difference, p-value and 95% CI) will be generated.

9.3.1.2. Missing Data Handling

No imputation for missing efficacy and safety data. Additional details for missing data handling will be provided in the SAP.

9.3.2. Primary Endpoints/Estimands Analysis

9.3.2.1. Definition of Endpoints

For Part A, the primary endpoint is incidence and severity of TEAEs as assessed by CTCAE.

For Part B, the primary endpoint is change in magnitude of IL-2 response pre- and post-GC in peripheral blood from baseline screening to Day 15.

For Part C, the primary endpoint is change in IL-2 from pre-GC to post-GC on Day 15 in participants treated with KAN-101 versus PBO.

9.3.2.2. Main Analytical Approach

For Part A, number and percent of participants with TEAEs will be summarized by: dose, SOC, PT, and severity.

For Part B, the primary endpoint will be descriptively summarized using estimand 1 (see Section 9.1.1.1) for FAS. No statistical hypothesis testing.

For Part C, the primary endpoint, change in IL-2 from pre-GC to post-GC on Day 15 will be analyzed using ANOVA model as described in Section 9.1.1.2 and Section 9.3.1.1.

- The main analysis of the primary endpoint will be based on Estimand 2 (see Section 9.1.1.2) using FAS.
- All statistical tests will be 2-tailed at a $\alpha = 0.05$.

9.3.2.3. Sensitivity Analysis

For Part C, the sensitivity analysis will be based on treatment policy estimand using FAS. Further details will be given in the SAP.

9.3.3. Secondary Endpoints Analysis

For Part A, PK concentration and PK parameters will be descriptively summarized by treatment group. The PK parameters to be assessed, their definition, and method of determination are detailed in Section 9.3.5. Actual PK sampling times will be used in the derivation of PK parameters.

For Part B and Part C,

- Number and percent of participants with TEAEs will be summarized by treatment, SOC, PT, and severity. Number of TEAEs (all-causality and treatment-related) and percent of participants with TEAEs will also be summarized by treatment period, treatment, SOC, PT, and severity.

- PK concentration and PK parameters will be descriptively summarized by treatment group.

9.3.4. Tertiary/Exploratory Endpoints Analysis

Results of exploratory endpoint analyses will be utilized for internal purposes and may not be described in the CSR.

For Part A,

- Change in magnitude of IL-2 response pre-and-post GC in in peripheral blood at Day 15 will be descriptively summarized by cohort.

- KAN-101 PK parameters, as data permit: AUC_{inf} (dn), AUC_{last} (dn), C_{max} (dn), CL, V, for analysis details see Section 9.3.5.

- Incidence of development of ADA during the study, for analysis details see Section 9.3.7.

For Part B,

- PRO will be summarized to track CeD symptoms over the duration of the study for FAS. Further details will be provided in the SAP.

- Change in magnitude of IL-2 response pre- and post-GC in peripheral blood from baseline (run-in) to GC at Weeks 12, 24, and 36 will be descriptively summarized by timepoint for FAS.

- Change in magnitude of IL-2 response pre- and post-GC in peripheral blood from Day 15 to Weeks 12, 24, and 36 will be descriptively summarized by timepoint for FAS as well.

- KAN-101 PK parameters, as data permit: AUC_{inf} (dn), AUC_{last} (dn), C_{max} (dn), CL, V, for analysis details see Section 9.3.5.

- Incidence of development of ADA during the study, for analysis details see Section 9.3.7.

For Part C,

- PRO will be analyzed using ANCOVA model by timepoint for FAS. Further details will be provided in the SAP.
- Change in circulating levels of IL-2 from pre-GC to post-GC at Weeks 12, 24, and 36 will be analyzed using ANOVA model by timepoint for FAS.
- Change in circulating levels of IL-2 from pre-dose to post dose on Days 1, 4, and 7 will be analyzed using ANOVA model by timepoint for FAS.
- Change in circulating levels of IL-2 pre- and post-GC from Day 15 to Weeks 12, 24, and 36 will be analyzed using ANOVA model by timepoint for FAS.
- KAN-101 PK parameters, as data permit: AUC_{inf} (dn), AUC_{last} (dn), C_{max} (dn), CL, V, for analysis details see Section 9.3.5.
- Incidence of development of ADA during the study, for analysis details see Section 9.3.7.

For Part B and Part C substudy,

- Change from baseline in histology (including, but not limited to, Marsh score, villous height crypt depth ratio, IEL counts) at Week 52 will be summarized by treatment for biopsy substudy.
- Correlation between histological state, symptomatic response (PRO data) and biomarker responses (IL-2) will be provided.

9.3.5. Pharmacokinetic Analysis

Actual PK sampling times will be used in the derivation of PK parameters. The plasma concentration of KAN-101 will be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual subject, mean, and median profiles of the plasma concentration-time data will be plotted by treatment group using actual (for individual) and nominal (for median) times respectively. Mean and median profiles will be presented on both linear and log scales.

Table 2. PK Parameters Analyzed

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{last} (dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$,

Table 2. PK Parameters Analyzed

Parameter	Definition	Method of Determination
		where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
AUC_{inf} (dn)	Dose normalized AUC_{inf}	AUC_{inf}/Dose
C_{max}	Maximum serum concentration	Observed directly from data
C_{max} (dn)	Dose normalized C_{max}	C_{max}/dose
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the loglinear -concentration time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CL[a]	Apparent systemic clearance	Dose/AUC_{last}
V[a]	Apparent volume of distribution	Dose/AUC_{inf}×k_{el}

a. If data permits

The PK parameters in Table 2 will be summarized descriptively by treatment group in accordance with sponsor data standards. Summary statistics will also include the geometric mean and coefficient of variation for all parameters except T_{max}. Where data permit, dose normalized (to a 1 mg dose) C_{max}, AUC_{inf}, and AUC_{last}, will be plotted against dose (using a logarithmic scale). The plot will include individual subject values and the geometric means for each dose. These plots will be used to determine the relationship between PK parameters and dose.

9.3.6. Safety Analyses

All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations for Part A and Part B separately. All safety analyses will be performed on the safety population.

9.3.7. Other Analyses

Immunogenicity assessments will be summarized descriptively.

Biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

Interim analyses may be conducted and results may be used to inform internal decisions regarding future study planning.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind (if applicable) as per the sponsor's SOPs will be documented and approved in a DSMB charter. In addition, the analysis details will be documented and approved in the SAP.

9.5. Sample Size Determination

It is anticipated that the study will enroll approximately 126 – 132 participants:

- Part A = 6-12 participants
- Part B = Approximately 16 participants
- Part C = Approximately 104 participants
- Biopsy Substudy (at applicable sites only) will enroll up to approximately 50% participants enrolled in Part B and up to approximately 50% participants enrolled in Part C.

There is no formal power calculation for the open-label Part A.

There is no formal power calculation for Part B.

In Part C, assuming the mean difference in the change from pre-GC to post-GC of log-transformed IL-2 levels on Day 15 is 2.37 between KAN-101 and PBO and the common standard deviation is 1.53, a sample size of 26 in each group will have 99% power, using a 2-group t-test with a 5%, 2-sided significance level. The Part C sample size is large enough to offer insight into the exploratory endpoints.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, the sponsor should be informed immediately.

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use a DSMB. The DSMB is independent of the study team and includes voting external members. The DSMB charter describes the role of the DSMB in more detail.

The DSMB will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DSMB will be forwarded to the appropriate authorized sponsor personnel for review and final decision. The sponsor will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

10.1.6. Dissemination of Clinical Study Data

The sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and other public registries and websites in accordance with applicable local laws/regulations. In addition, the sponsor reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by the sponsor in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

The sponsor posts clinical trial results on www.clinicaltrials.gov for Kanyos Bio, Inc.-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

The sponsor posts clinical trial results on EudraCT/CTIS for Kanyos Bio, Inc.-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

Documents within marketing applications

The sponsor complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

The sponsor provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. The sponsor will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor or sponsor's designee (Pfizer).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study -site closure visit has been performed.

The investigator may initiate study -site closure at any time upon notification to the sponsor or designee (Pfizer) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

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

10.1.11. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the ISF or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical

questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

Table 3. Protocol Required Safety Laboratory Assessments

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

a. aPTT and INR tests are performed in Part A only.
b. **Part C only:** At times indicated in the SoA (Section 1.3.3).
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
d. For confirmation of postmenopausal status only.
e. A serum pregnancy test is required at screening. Following screening, local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β–hCG for female participants of childbearing potential.
f. For re-screening, the HLA does not need to be repeated and CeD serology (the tTG and DGP antibody tests) should only be repeated if >3 months have elapsed from previous assessment.
g. For tTG, a result of ≤ 10 U/mLi will be considered negative or weak positive. For DGP, a result of <30 U/mL will be considered negative or weak positive.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Laboratory/analyte results that could unblind the study and have been collected for the purpose of the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE: Is associated with accompanying symptoms. Requires additional diagnostic testing or medical/surgical intervention. Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Kanyos Bio, Inc. product of an infectious agent, pathogenic or nonpathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Kanyos Bio, Inc. product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs or SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE): is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor/Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the categories listed below (as defined by the NCI CTCAE system).

GRADE	Clinical Description of Intensity
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING; urgent intervention indicated
5	DEATH RELATED TO AE

Further details regarding the CTCAE are presented in Appendix 10.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Pfizer Safety . However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pfizer Safety.**
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by Pfizer Safety. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor/Pfizer Safety, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to Pfizer Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor Safety via an Electronic DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT. • If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Sponsor Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria (Parts A and B)

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 21 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

  PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- The male participant should be advised of the benefit for a WOCBP partner using a highly effective method of contraception with a failure rate of <1% per year, as described in Section 10.4.4.

10.4.2. Female Participant Reproductive Inclusion Criteria (Parts A and B)

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

- A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for 21 days after the last dose of study intervention; and (c) at least 1 of the following conditions applies:

  - Is not a WOCBP (see definition in Section 10.4.3).

    OR

  - Is a WOCBP and agrees to use a contraceptive method that is highly effective (failure rate of <1% per year) with low user dependency during the intervention period and agrees to use it for at least 21 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 21 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

    - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

    - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for specified genetic analysis (see Section 8.6.1) will not be stored beyond the completion of this study (eg, CSR finalization), unless the participant agrees to optional additional research on these samples.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

(Inker et al, 2021)

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 Ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and the sponsor study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.9. Appendix 9: Infusion-Related Reactions

Participants will be monitored in the clinic for 4 hours following IV study drug administration for IRR. IRR may include, but are not limited to: erythema, induration, ecchymosis, pain, and pruritus.

If an IRR occurs during study intervention 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 participant 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 study intervention infusions.

- **Grade 2 (moderate):** Slow infusion rate 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 participant 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 study intervention 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 participant is deemed stable.

    - If the reaction has not resolved within 6 hours, the remainder of the infusion will not be administered and study intervention will be permanently discontinued.

    - Following the completion or termination of a restarted infusion due to an IRR:

        - All participants 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 recommended at least 30 min prior to future study intervention 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 30-minutes-per dose rate as outlined in Section 6.1.1.

    - If second occurrence of Grade 3 or greater IRR, permanently discontinue study intervention.

- **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 study intervention.

10.10. Appendix 10: Common Terminology Criteria For Adverse Events

CTCAE Terms

AEs are defined in Appendix 3. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE term as a MedDRA Lowest Level Term. The latest available version of CTCAE will be used (NCI NIH, 2017).

Definitions

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

Grades

Grade refers to the severity of the AE and are specified in Appendix 3. Further details are provided below. CTCAE v5.0 grades for GI disorders frequently observed in the FIH study KAN-101-01 are provided in Table 4.

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 is therefore not an opinion.

Table 4. CTCAE v5.0 Grades for GI Disorders Observed in KAN-101-01 (FIH Study)

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Abdominal pain	Mild pain	Moderate pain, limiting instrumental ADL	Severe pain; limiting selfcare ADL	-	-
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting selfcare ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL	Life-threatening consequences; urgent intervention indicated	Death
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Flatulence	Mild symptoms; intervention not indicated	Moderate symptoms; psychosocial sequelae	-	-	-

Activities of Daily Living

* 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 bed ridden.

10.11. Appendix 11: Marsh Criteria for Diagnosis of Celiac Disease

Diffuse intraepithelial lymphocytosis, normal villi, consistent with celiac disease	Marsh type 1
Diffuse intraepithelial lymphocytosis and crypt hyperplasia, consistent with celiac disease	Marsh type 2
Partial villus atrophy, crypt hyperplasia and intraepithelial lymphocytosis, consistent with celiac disease	Marsh type 3a
Subtotal villus atrophy, crypt hyperplasia and intraepithelial lymphocytosis, consistent with celiac disease	Marsh type 3b
Total villus atrophy, crypt hyperplasia and intraepithelial lymphocytosis, consistent with celiac disease	Marsh type 3c
Villus atrophy, crypt hypoplasia and intraepithelial lymphocytosis, consistent with celiac disease	Marsh type 4

Lagana & Bhagat. 2019

10.12. Appendix 12: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 2 (06 Nov 2023)

Document	Version Date	Summary of Changes	Rationale for Changes
Protocol Amendment 2	06 November 2023	Extended the screening period to 28 days in Part B prior to run-in GC in following sections: • Synopsis, • Schema (Section 1.2.2), • SoA (Section 1.3.2) for Part B, • Overall Design Part B (Section 4.1.2).	Screening window is extended to 28 days to accommodate potential longer time needed for HLA genotyping and CeD serology.
		Clarified fasting requirement on the days for safety laboratory and GC in following sections: • SoA (Section 1.3.2) in Part B, • Section 8.2.1 and 8.3.4	To provide consistency and clarity for fasting requirements for safety laboratory tests and GC.
		Clarified urine pregnancy tests collected prior to run-in GC, and that urine pregnancy test prior to EGD should be performed per local practice guidelines in SoA (Section 1.3) in Part B.	Text clarification for urine pregnancy test requirements.
		Changed cutoff of tTG in inclusion criterion #4 from <2x ULN to ≤10 U/mL in sections: • Synopsis • Inclusion Criteria (Section 5.1).	To provide clear definition for 'negative or weak positive' based on central laboratory cutoff.
		Clarified using premedication for study intervention in	Allow permitted premedication for

Document	Version Date	Summary of Changes	Rationale for Changes
		Section 6.1.1 and 6.9.3. in Part B.	management of AEs during study intervention.
		Inserted Marsh criteria for diagnosis of celiac disease in Appendix 10.11, citation to Appendix 10.11 in Inclusion Criterion #2and the added reference to Section 11, References.	The insertion provides the reference to Marsh score.
		Other minor administrative changes for clarification.	Provide consistency throughout the document.

Amendment 1 (21 Jun 2023)

Document	Version Date	Summary of Changes	Rationale for Changes
Protocol Amendment 1	16 June 2023	Changes made to the following sections of the protocol to Part A and Part B of the study design to eliminate 6.0 mg/kg in Part A as dose Cohort 3, and define 0.6 mg/kg, 1.2 mg/kg, and 3.0 mg/kg as active study drug arms and placebo in Part B; • Synopsis, • Study Design Schema, • Overall Design (4.1), • Justification for Dose (4.3), • Study Intervention(s) Administered (6.1), and • Statistical Considerations (9) Changes.	Newly emerging clinical data from Part A supports progression to Part B following completion of 3.0 mg/kg cohort in Part A and safety review by DSMB. The Sponsor has made revisions, to the study design to eliminate the 6.0 mg/kg dose cohort in Part A and confirm 0.6 mg/kg, 1.2 mg/kg, 3.0 mg/kg and placebo as treatment arms for Part B of the study.
		Clarification of PK sampling time points in Schedule of Activities.	Changes in PK sampling notes in both Part A and B to clarify the use of infusion

Document	Version Date	Summary of Changes	Rationale for Changes
			start time as reference timepoint for post-dose PK collections.
		Clarify requirements for EGD, HLA genotyping and CeD serology in rescreening participants in Schedule of Activities, Section 5.4, Screen Failures, Section 8.2.4 Esophagogastroduodenoscopy With Biopsy, and Appendix 10.2 Clinical Laboratory Tests	Changes made in these sections to be consistent throughout the protocol.
		Remove requirements that are not applicable for the study in Section 6.5 for Study Intervention Compliance	Removed requirements that are not applicable with the current version of IPM.
		Other administrative changes throughout the document	Administrative Changes to make clarifications and consistencies throughout the document.

10.13. Appendix 13: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
ADA	anti-drug antibodies
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf} (dn)	dose normalized AUC_{inf}
AUC_{inf}	area under the plasma-concentration curve from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
AUC_{last} (dn)	dose normalized AUC_{last}
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BL	baseline
BP	blood pressure
bpm	beats per minute
CDSD	Celiac Disease Symptom Diary
CeD	celiac disease
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{last}	last quantifiable concentration
C_{max}	maximum plasma concentration
C_{max} (dn)	dose normalized C_{max}
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CL	apparent systemic clearance
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CSR	Clinical Study Report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CV	cardiovascular
DBP	diastolic blood pressure
DCT	data collection tool
DGP	deamidated gliadin peptide(s)
DILI	drug-induced liver injury
DLT	dose limiting toxicity(ies)
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DU	dispensable unit
EAE	experimental autoimmune encephalomyelitis
EC	ethics committee
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EFD	embryonic fetal development
EGD	esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAS	full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FSH	follicle-stimulating hormone
FU	follow-up
GC	gluten challenge
GCP	Good Clinical Practice
GFD	gluten-free diet
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	good laboratory practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Term
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLA-DQA1 and HLA-DQB1	human leukocyte antigen loci
HLA-DQ2.5	human leukocyte antigen loci encoded by HLA-DQA1*05 and HLA-DQB1*02 (homozygotes or heterozygotes) genotype
HLA-DQ8	human leukocyte antigen serotype with the HLA-DQ serotype group
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
IBS	Irritable Bowel Syndrome
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IEL	intraepithelial lymphocytes
IgA	immunoglobulin A
IgG	immunoglobulin G
IL-2	interleukin-2
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
ISF	Investigator Site File
IV	intravenous(ly)
k_{el}	elimination rate constant
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LSM	least-squares mean
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MQI	medically qualified individual
MTD	maximum tolerated dose
N/A	Not Applicable

Abbreviation	Term
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NTD	non-tolerated dose
OH	orthostatic hypotension
OTC	over the counter
PBMC	peripheral blood mononuclear cell
PBO	placebo
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Primary Investigator
PK	pharmacokinetic(s)
PO	by mouth; oral(ly)
PR	pulse rate
PRO	patient reported outcomes
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	Preferred Term; prothrombin time
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
Rand.	Randomization
RBC	red blood cell
RNA	ribonucleic acid
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	serum creatinine
Scys	serum cystatin C
SM	safety margin
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{½}$	terminal phase half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse events
TPN	total parenteral nutrition
tTG	transglutaminase

Abbreviation	Term
T_{max}	time to reach C_{max}
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
V	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

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