Title: Assessment of Immune Activation and Tolerance in Celiac Disease During Gluten Challenge

NCT Number: NCT03409796

Protocol Approve Date: 06 October 2017

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TAKEDA PHARMACEUTICALS

PROTOCOL

Assessment of Immune Activation and Tolerance in Celiac Disease During Gluten Challenge

Trial Identifier:	TIMP-GLIA-5001
Compound:	Not applicable
Date:	06 October 2017
Version/Amendment Number:	Initial

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1.0 TRIAL SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. 35 Landsdowne St, Cambridge, MA 02139	**Compound:** Not applicable
Trial Identifier: TIMP-GLIA-5001	**Phase:** Not applicable
Protocol Title: Assessment of Immune Activation and Tolerance in Celiac Disease During Gluten Challenge	
Trial Design: This is a randomized, double-blind, 2-part gluten challenge trial in subjects with celiac disease (CeD) who are HLA-DQ2.5 and/or HLA-DQ8 positive and have been on a gluten-free diet (GFD) for at least 6 months. Subjects will be enrolled until a maximum of approximately 20 complete the gluten challenge with follow up endoscopy.	
Trial Primary Objective: To characterize changes in gluten-specific T cells and pathology in the small intestine with specific focus on biomarkers likely to change with therapeutic CeD treatment. **Secondary Objectives:** To assess correlation between gluten-specific blood T cells and standard CeD histological assessments. To assess changes from Baseline in gluten-specific T cells in blood.	
Trial Subject Population: Subjects will be healthy other than having CeD, as determined by the investigator. Each subject in the trial will be aged 18 to 75 years, inclusive, have biopsy-confirmed disease that is clinically inactive with negative CeD serology, have followed a GFD for ≥6 months as reported by the subject, and be HLA-DQ2.5 and/or HLA-DQ8 positive.	
Planned Number of Subjects: Up to approximately 20 to complete the trial	**Planned Number of Sites:** 1 to 3
Dose Levels: Gluten 3 g (Group A, n≤14) Gluten 10 g (Group B, n≤14)	**Route of Administration:** Oral
Duration of Treatment: 14 days	**Planned Trial Duration:** Approximately 10 weeks
Main Criteria for Inclusion: In order to be eligible for trial participation, subjects must: 1. Be a man or woman aged 18 to 75 years, inclusive, at the time of the Screening Visit. 2. Have a body mass index ≥18 and ≤30 kg/m^2 and a body weight >50 kg at the Screening Visit. 3. Agree to make every effort to avoid pregnancy from the time of signing the informed consent throughout the duration of the trial and for at least 3 months after conclusion of trial participation, if the subject is a woman of childbearing potential and sexually active with a nonsterilized male partner. 4. Have well controlled biopsy-proven CeD, compliant with a GFD for ≥6 months preceding Screening, with resolution of CeD symptoms, normalization of CeD serology, and in the judgment of the investigator, have inactive or minimally-active disease. 5. Be HLA-DQ2.5 and/or HLA-DQ8 positive, as assessed at Screening. If subjects have already been genotyped, then results from previous testing may be used in lieu of genotyping at Screening.	

Main Criteria for Exclusion:

Subjects must be excluded from the trial if they have:

1. A history of any abdominal or pelvic surgery <3 months before trial enrollment; prior surgery involving the luminal gastrointestinal tract (eg, cholecystectomy, appendectomy, and hysterectomy) are permitted if performed >3 months before trial enrollment.
2. Positive IgA anti-tissue transglutaminase, IgA anti-deamidated gliadin peptide (DGP), and IgG DGP serologies at Screening.
3. Inflammatory gastrointestinal disorders or autoimmune diseases other than CeD or autoimmune thyroid disease.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the trial is change from Baseline in small intestine histology based on standard CeD histological assessments (intraepithelial lymphocyte counts and villus height to crypt depth ratio [Vh:Cd] measures).

Secondary endpoints will be assessed through evaluation of the following parameters:

- Correlation between gluten-specific blood T cells and standard CeD histological assessments.
- Changes from Baseline in gluten-specific T cells in blood, based on functional assays and/or gluten-specific T cell receptor (TCR) staining.

Statistical Considerations:

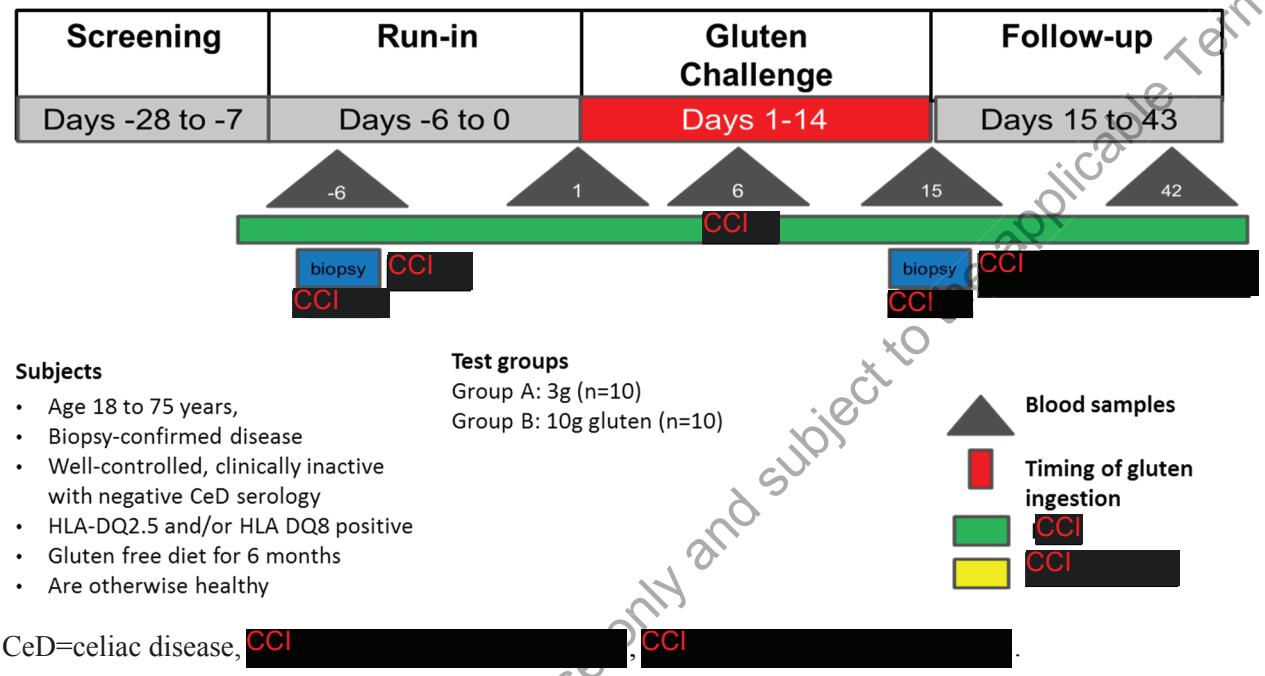
Overall, a total of approximately 20 subjects will be enrolled and randomly assigned into 1 of 2 groups: 3 g gluten/day (Group A, n≤14), or 10 g gluten/day (Group B, n≤14). In Part 1 of the trial, 12 subjects will be randomly assigned into each group in a 1:1 ratio. After interim analysis, if a 2-sided paired t-test measuring change from Baseline in Vh:Cd is not greater in magnitude than 2.63 in the initial 12 subjects, or if a 2-sided paired t-test measuring change from Baseline in T cell markers as measured by tetramers or similar TCR staining reagents (if performed) is not greater than 2.80, then additional subjects will be enrolled to enter Part 2 of the trial. A paired t-test will be performed comparing subjects in groups A and B, and if it is significant at a 5% level, then additional subjects will be enrolled into the group with the greater change in Vh:Cd. Otherwise, subjects will be enrolled equally into groups A and B.

Sample Size Justification:

The number of subjects was selected to detect a change in Vh:Cd and T cell markers with 80% power at the interim analysis and with >99% by the final analysis, as well as to allow estimation of biomarker differences for secondary and exploratory endpoints. A single analysis with 12 subjects has 92% power to detect a change in Vh:Cd before and after gluten challenge, and a 99% power to detect a change in T cell markers. This was converted to a group sequential design such that the interim analysis with 12 subjects has 84% power to detect a change in Vh:Cd and 95% power to detect a change in T cell markers, for an overall power of 80% for the interim analysis.

2.0 TRIAL SCHEMATIC

Figure 2.a Trial Schematic



CeD=celiac disease, CCI [redacted], CCI [redacted].

3.0 SCHEDULE OF TRIAL PROCEDURES

Table 3.a Schedule of Trial Procedures

Assessment (a)	Screening	Run-in	Gluten Challenge		Follow-up/Early Termination		
	Days -28 to -7	Days -6 to 0	Days 1 to 14		Days 15 to 43		
Day	-28 to -7	-6 to 0	1 (Predose)	6	15	42	43
Hours postdose			4				
Location	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Administrative Procedures							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history/demographics	X						
Prior and concomitant medications	X						
Treatment Assignment and Administration							
Random assignment to trial treatment			X				
Gluten dosing (b)			X	X			
Clinic Procedures and Assessments							
Physical examination	X				X		
Heart rate and blood pressure (systolic and diastolic)	X				X		
Respiratory rate and temperature (oral at the floor of the mouth or tympanic)	X				X		
Height	X						
Weight	X				X		
Body mass index	X						
Adverse event assessment	X						
CCI [redacted]							
Endoscopy (d)		X			X		
Laboratory Procedures and Assessments							
Serum chemistry	X						
Hematology	X						
Serum pregnancy	X	X (e)					
Urine drug screen	X						

Footnotes are on last table page.

Table 3.a Schedule of Trial Procedures (continued)

Assessment (a)	Screening	Run-in	Gluten Challenge		Follow-up/Early Termination		
	Days -28 to -7	Days -6 to 0	Days 1 to 14		Days 15 to 43		
Day	-28 to -7	-6 to 0	1 (Predose)	6	15	42	43
Hours postdose			4				
Location	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Biomarker Evaluations							
Fresh duodenum tissue biopsy (FFPE)		X			X		
Frozen duodenum tissue biopsy		X			X		
Blood sample for HLA typing	X						
Blood sample for immunophenotyping, TCR staining, and ELIspot		X	X	X	X		
Blood for IgA tTG, IgA DGP, and IgG DGP serology	X		X		X	X	
Serum sample for protein (cytokines, chemokines, other)		X	X (f)	X	X	X	
Blood sample for RNA		X	X (f)	X	X	X	
Blood sample for DNA		X	X	X	X		

DGP=anti-deamidated gliadin peptide, FFPE=formalin-fixed paraffin embedded, CCI [redacted], TCR=T cell receptor, tTG=anti-tissue transglutaminase, CCI [redacted]

(a) Unless otherwise specified, procedures should be performed as close to the day and time indicated as possible.

(b) Gluten will be ingested daily on Days 1 to 14, inclusive, at approximately the same time each day, and without regard to food. On Day 1, subjects do not need to be fasting and will take their entire single dose in the clinic after predose blood samples have been drawn. On Days 2 through 5 and Days 7 through 14, gluten will be taken by the subject at home. On Day 6, gluten may be taken at home or in the clinic.

(c) CCI [redacted]

(d) The initial endoscopy can be performed at any time during Run-in before the first gluten dose. The second endoscopy can occur at any time on Day 15.

(e) Not needed if ≤7 days since screening pregnancy test.

(f) Samples taken at predose and 4 hours postdose.

4.0 INTRODUCTION

Celiac disease (CeD) is a common immunological disorder with an estimated prevalence of approximately 0.5% to 1% in different parts of the world [1]. Celiac disease develops in genetically predisposed subjects as a consequence of an abnormal T cell response to wheat prolamin protein, predominately gliadin, and results in diarrhea, constipation, and other gastrointestinal symptoms; increased intestinal permeability, malabsorption, and occult gastrointestinal bleeding; and systemic manifestations including secondary autoimmunity, infertility, dermatitis herpetiformis, and malignancy [2,3].

Clinical trials that include gluten challenge are used to test the effectiveness of therapies designed to prevent immune response to gluten in subjects with CeD [4,5]. A variety of serological and biopsy-based biomarkers have been used in clinical studies to characterize individual pathological constituents of CeD and overall disease progression.

4.1 Background

Serological biomarkers respond slowly to ongoing changes in the intestine and are better used for disease diagnosis rather than as a means to monitor therapeutic changes [6]. Changes in intestinal tissue morphology such as measures of villus height to crypt depth ratio (Vh:Cd) and intraepithelial lymphocyte (IEL) counts are the standard method for diagnosing and evaluating progression of CeD, but require invasive biopsies and do not provide data to help understand the underlying mechanisms that mediate these changes.

Patients with CeD express the major histocompatibility complex (MHC) Class II molecules, HLA-DQ2 or HLA-DQ8. These molecules are expressed on antigen-presenting cells (APC) and are capable of effectively binding and presenting deamidated gliadin peptides to T cells. Although all CeD patients are HLA-DQ2 and/or HLA-DQ8 positive, these proteins are required, but not sufficient, for development of disease [7]. In addition, patients must have CD4+ T cells that express a T cell receptor (TCR) that binds antigen in the context of these MHC Class II molecules. Highly antigenic epitopes of gliadin have been defined and the TCRs that bind these epitopes have been sequenced [8]. The genes that encode the TCRs differ, but TCR proteins share common sequences that allow them to bind specific gliadin epitopes tightly and respond to antigen stimulation by proliferating, producing cytokines, and starting a cascade of events leading to the destruction of intestinal villi [9-11]. B cells may also function in this process both as APCs and antibody-producing cells [12].

In this clinical trial, a number of different blood and intestinal biomarkers will be evaluated and how they change in subjects with CeD after gluten challenge. Included are commonly used serological and histological markers as well as newer, less invasive and/or more informative methods. The results of this trial will provide a data set that will help design future interventional studies in CeD.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

4.2 Rationale for the Proposed Trial

This 14-day gluten challenge trial is being conducted to characterize and correlate the number of peripheral blood biomarkers, visually assessed macroscopic changes, symptoms, and small intestine pathology with a specific focus on markers that are likely to change with CeD treatment. The results of this trial will be used to select the biomarker approaches appropriate for future clinical development.

4.3 Benefit/Risk Profile

As this trial does not include a therapeutic arm and will be conducted on otherwise healthy subjects with well-controlled CeD, there is no expected clinical benefit to the trial participants. Potential risks are based on symptoms related to gluten exposure and testing related to trial endpoints. These include the following:

- Phlebotomy: there is minimal risk associated with phlebotomy (limited to <500 mL) in otherwise healthy adults.
- Endoscopy with duodenal biopsy: endoscopy with duodenal biopsy is a common gastrointestinal procedure. Risks include those related to procedural sedation, the endoscopic procedure, and the biopsies. Cumulatively, the risks of upper endoscopy are estimated to be <0.5% (Complications of diagnostic colonoscopy, upper endoscopy, and enteroscopy [13]. All subjects enrolled in this study will have undergone at least 1 previous uncomplicated endoscopy with biopsy. Clinical evaluation of subjects before endoscopy will be completed according to established site protocols.
- CCI
- [redacted]

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Peripheral T cell markers can be used to accurately evaluate CeD activity after a gluten challenge of 3 g gluten/day for 3 days.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

The primary objective of the trial is to characterize changes in gluten-specific T cells and pathology in the small intestine with specific focus on biomarkers likely to change with therapeutic CeD treatment.

5.2.2 Trial Secondary Objectives

The secondary objectives of this trial are as follows:

- To assess correlation between gluten-specific blood T cells and standard CeD histological assessments.
- To assess changes from Baseline in gluten-specific T cells in blood.

5.2.3 Trial Exploratory Objectives

CCI

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoint

The primary endpoint of the trial is change from Baseline in small intestine histology based on standard CeD histological assessments (IEL counts and Vh:Cd measures).

5.3.2 Secondary Endpoints

Secondary endpoints are as follows:

- Correlation between gluten-specific blood T cells and standard CeD histological assessments.
- Changes from Baseline in gluten-specific T cells in blood, based on functional assays and/or gluten-specific TCR staining.

5.3.3 Exploratory Endpoints

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a randomized, double-blind, 2-part gluten challenge trial in subjects with CeD who are HLA-DQ2.5 and/or HLA-DQ8 positive and have been on a gluten-free diet (GFD) for at least 6 months. Subjects will be enrolled until a maximum of approximately 20 subjects complete the gluten challenge and follow-up endoscopy.

The trial will consist of 4 periods: Screening (Days -28 to -7), Run-in (Days -6 to 0), Gluten Challenge (Days 1-14, inclusive), and Follow-up (Days 15-43).

After signing the informed consent form (ICF), subjects will be enrolled and randomly assigned to 1 of 2 treatment groups: 3 g gluten/day or 10 g gluten/day. Both groups will be treated concurrently. Subjects receiving 10 g gluten/day will be able to reduce their dose to 3 g gluten/day after Day 3 if needed because of severity of symptoms. Dose reduction will be managed by an unblinded qualified staff member not directly involved in the treatment or clinical evaluation. A complete gluten challenge requires that at least 12 of the 14 doses of gluten are taken before the follow-up endoscopy.

Subjects will be genotyped at Screening. If a subject has already been genotyped, results from previous testing may be used in lieu of genotyping at Screening. Symptoms will be measured daily by subjects using the CDSD. During Run-in, each subject will undergo a single, traditional endoscopy, and blood sampling to establish baseline values. CCI [redacted] During Gluten Challenge, all subjects will undergo periodic blood sampling. The day after completion of the gluten challenge, CCI [redacted] Endoscopy will include video when feasible. During Follow-up, subjects will complete the CDSD, provide an additional blood sample, and undergo periodic CCI [redacted].

6.2 Dose Escalation

Not applicable.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

The design of this trial will allow identification of blood and tissue changes induced by gluten challenge that occur as a result of CeD. Expected in most subjects are changes in blood cell numbers and types and cytokines and proteins, intestinal changes in the types and number of infiltrating cells, and changes in the intestinal epithelium that are visible CCI [redacted].

6.3.1.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

6.3.1.2 Rationale for Biomarkers

The sponsor is exploring compounds for which the mechanism of action is to reduce/eliminate the gluten-specific effector T cell response and induce T cell tolerance. The biomarkers chosen for this trial will allow profiling of the inflammatory changes that occur in the small intestine as gluten induces an immune response, and to correlate these changes with those occurring in the blood. This set of markers will inform future studies in the sponsor's CeD program.

The sponsor will conduct future biomedical research on specimens collected during this trial. This research may include genetic analysis (DNA), gene expression profiling (RNA), proteomics, metabolomics, and/or measurements of other analytes.

6.3.2 Rationale for Gluten Dose

The gluten doses are expected to be high enough to elicit an acute immune response in most subjects with tolerable symptoms [6]. The 3 g gluten/day dose level was selected based on published reports [5,6] that show similar dose levels are tolerable and result in histological changes in the small intestine; however, other studies have suggested a dose response in histological changes [12]. The 10 g gluten/day dose level was selected to increase the chances of seeing detectable levels of gluten-specific T cells in the blood. Both groups will be treated concurrently.

6.3.3 Rationale for Endpoints

6.3.3.1 Primary Endpoint: Histological Assessments

Gluten challenge followed by endoscopic biopsy of the duodenum and calculation of the Vh:Cd, coupled with enumeration of the number of IELs per 100 enterocytes, is a standard method for diagnosing CeD, especially in subjects compliant with a GFD [6]. The IELs include cytotoxic CD8+ T cells that increase with gluten exposure and may mediate epithelial damage [14]. Change in Vh:Cd is a measure of the epithelial damage, specifically of villus atrophy and compensatory crypt hyperplasia [15].

In this trial, 8 biopsies will be taken per endoscopy and used for histology and other analyses, which may include 12-marker IHC and transcriptional analysis. An experienced gastrointestinal pathologist will act as a central reader and perform all assessments, for example, Vh:Cd and QMarsh semiquantitative assessment. Some samples may be archived and used for future biomedical research.

6.3.3.2 Secondary Endpoint: T cell Markers

One approach to measuring drug response in future interventional clinical trials in subjects with CeD is to quantify changes in the number or function of gluten-specific T cells either directly using ELISpot or staining gluten-specific TCR, or alternatively indirectly using TCR sequencing (Section 6.3.3.3) [16]. In this trial, assay sensitivity to gluten treatment and technical feasibility of

each assay will be evaluated to make an informed decision on how to use these assays in future trials.

Functional T Cell Marker (Blood Only)

To measure T cell function, an ELISpot assay that will evaluate gluten-specific T cell cytokine production (such as IL-10 and interferon-γ [INF-γ]) may be used. This assay has been used by others to characterize T cell responses to gluten in CeD [17]. For the purposes of this trial, this assay shows a functional T cell response. In comparison, fluorescently labeled TCR-staining reagents (such as tetramers/dextramers) show T cell binding to gluten in the context of MHC class II, but do not predict the results of downstream signaling; TCR profiling shows only the expansion of subsets of T cells with specific TCR associated with gluten binding. The ELISpot assay will be correlated with TCR staining and/or TCR profiling to get a clearer picture of antigen-specific T cell changes after gluten challenge.

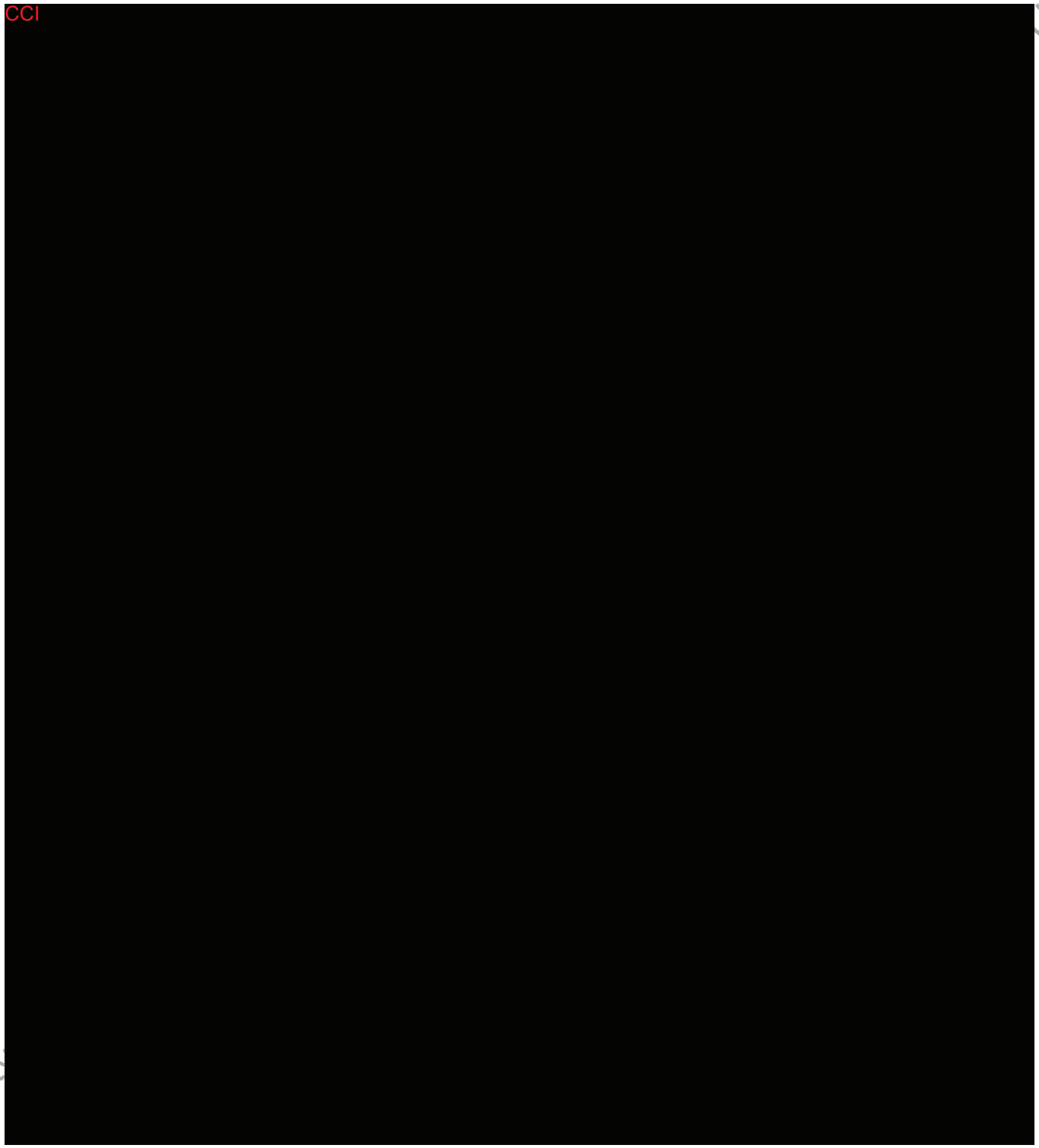
Antigen-Specific T Cells (Flow Cytometry Gluten-Specific–TCR Staining Reagents [Blood])

Flow cytometry may be used for identifying and quantifying gluten-specific CD4+ T cells using specific gluten-derived antigens bound to MHC Class II molecules. Either dextramers or tetramers may be used. Dextramers have a function similar to tetramers but tend to have higher affinity for the TCR because unlike tetramers, which are composed of 4 MHC Class II molecules, dextramers are composed of 10 or more MHC Class II molecules on a dextran backbone.

6.3.3.3 Exploratory Endpoints (Biomarkers)

CCI

CCI



6.3.3.4 Future Biomedical Research (Unplanned Exploratory Biomarker Research)

Archival biopsy (FFPE and frozen tissue), blood cells, serum, RNA, and DNA may be stored and assessed for additional biomarkers.

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, the critical procedure is endoscopy performed before and after gluten challenge. Endoscopy can be performed any day during Run-in before gluten challenge and anytime on Day 15 after gluten challenge. In addition, 4 hours after gluten dosing on Day 1, blood will be collected for transcriptional analysis and analysis of serum cytokines and other proteins. CCI will be performed as described in Section 9.3.5.1.

- All other procedures should be completed as close as possible, either before or after the prescribed/scheduled time.
- The order of priority can be changed during the trial with joint agreement of the investigator and the sponsor.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is an assessment of gluten challenge in humans with CeD. This protocol is written with some flexibility to accommodate the exploratory nature of this clinical trial. As such, some alterations from the currently outlined dose may be permitted based on newly available data, but the maximum daily dose detailed in Section 4.1 may not exceed those currently outlined. Modifications to the dose of gluten, dosing regimen, and/or clinical or laboratory procedures may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Modifications may include the following:

- Decrease in the dose of gluten administered.
- Additional subjects may be added after the interim analysis so that there are 20 subjects who complete the gluten challenge and second endoscopy.
- Decrease in the duration of gluten administration (eg, number of days).
- CCI [redacted]

The sampling scheme currently outlined in the protocol may be modified during the trial based on newly available data. If indicated, these collected samples may also be assayed in an exploratory manner for additional biomarkers.

Up to an additional 50 mL of blood may be drawn for biomarker analyses. This may include repeat samples or modified time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial.

The timing of planned procedures for assessment of safety procedures (eg, vital signs, safety laboratory tests) currently outlined in the protocol may be modified during the trial based on newly available safety or tolerability data. These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatinine kinase to serum chemistry panel that was already drawn).

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) at the discretion of the investigator.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The overall trial begins when the first subject signs the trial ICF.

6.5.2 Definition of End of the Trial

The overall trial ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the trial, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.5.3 Definition of Trial Completion

The trial will be considered completed for each subject after they attend the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact),

discontinue from the trial, or are lost to follow-up (ie, the investigator is unable to contact the subject).

6.5.4 Definition of Trial Discontinuation

Trial discontinuation may occur because of nonsafety reasons, such as:

- A finding (eg, biologic targets) from another nonclinical or clinical trial using the trial treatment(s).
- Data from methodology(ies) used in this trial become available.
- Low enrollment.

Early trial termination may occur because of unanticipated concerns of safety to the trial subjects arising from clinical or nonclinical trials with the trial treatment(s), or methodology(ies) used in this trial.

6.5.5 Criteria for Premature Termination or Suspension of a Site

6.5.5.1 Criteria for Premature Termination or Suspension of a Site

The trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.5.5.2 Procedures for Premature Termination or Suspension of a Site

In the event that the sponsor, an IRB, or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Understand the trial procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all trial procedures and restrictions.
3. Be a man or woman aged 18 to 75 years, inclusive, at the Screening Visit.
4. Have a body mass index (BMI) ≥18 and ≤30 kg/m2 and a body weight >50 kg at the Screening Visit.
5. Be a nonsmoker who has not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before Day 1 gluten administration.
6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, and vital sign measurements performed at the Screening Visit and before random assignment to trial treatment.
7. Agree to make every effort to avoid pregnancy from the time of signing the informed consent throughout the duration of the study and for at least 3 months after conclusion of study participation, if is a woman of childbearing potential and sexually active with a nonsterilized male partner.
    a) A woman is considered a woman of childbearing potential if she is fertile following menarche until becoming postmenopausal or permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) Standard methods of birth control are acceptable and may include hormonal contraceptives, true sexual abstinence, use of female and male condoms together, or cap/diaphragm/sponge without spermicide and without condom.
8. Have well-controlled biopsy-proven CeD, compliant with a GFD for ≥6 months preceding Screening, with resolution of CeD symptoms, normalization of CeD serology, and in the judgment of the investigator, have inactive or minimally-active disease.
9. Be HLA-DQ2.5 and/or HLA-DQ8 positive, assessed at Screening. If subjects have already been genotyped, results from previous testing may be used in lieu of genotyping at Screening.

10. Be willing to delay a planned procedure involving the use of powerful electromagnetic fields (eg, magnetic resonance imaging), CCI [redacted].
11. Not undergo CCI [redacted] if has an implanted electromedical device or a swallowing disorder.
12. Not undergo CCI [redacted] if has a contraindication to the device or procedure as per reference information.

7.2 Exclusion Criteria

Subjects must be excluded from the trial if they meet any of the following criteria:

1. Have a history of clinically significant endocrine, cardiovascular, hematological, hepatic, immunological (other than CeD or autoimmune thyroid disease), renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or disease.
2. Have participated in another investigational trial within 4 weeks before Screening. The 4-week window will be derived from the date of the last previous trial procedure and/or any adverse event (AE) related to the previous trial, to the Screening Visit of the current trial.
3. Are an employee or immediate family member (eg, spouse, parent, child, or sibling) of the sponsor.
4. Have a history of cancer (malignancy) other than nonmelanoma skin cancer.
5. Have a history of significant multiple and/or severe allergies (eg, latex allergy).
6. Are a woman who is lactating/breastfeeding.
7. Have had major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 8 weeks before the first dose of gluten.
8. Are unable to refrain from or anticipate the use of any unapproved medication, including prescription drugs, nonprescription drugs, and herbal remedies, beginning approximately 7 days before administration of the initial dose of gluten and continuing throughout the trial until the Follow-up Visit. There may be certain medications that are permitted, as described in Section 9.1.4.
9. Consume excessive amounts of coffee, tea, cola, energy drinks, or other caffeinated beverages per day. An excessive amount is defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine).
10. Have a positive drug screen.
11. Have a history of drug abuse (defined as any illicit drug use) or a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: 354 mL/12 ounces of beer, 118 mL/4 ounces of wine, or 29.5 mL/1 ounce per day of distilled spirits.

12. Have a history of any abdominal or pelvic surgery <3 months before trial enrollment; prior surgery involving the luminal gastrointestinal tract (cholecystectomy, appendectomy, and hysterectomy) are permitted if performed >3 months before trial enrollment.
13. Have positive IgA tTG, IgA DGP, and IgG DGP serologies at Screening.
14. Have inflammatory gastrointestinal disorders or autoimmune diseases other than CeD or autoimmune thyroid disease.
15. Have known or suspected gastrointestinal obstructions, strictures, or fistulas based on the clinical picture or pre-procedure testing and profile of the CCI [redacted].
16. Endoscopy and intestinal biopsy are contraindicated.

7.3 Excluded Medications, Supplements, Dietary Products

Subjects should avoid excessive use of steroids, immunosuppressants, and anticoagulants beginning approximately 7 days before administration of the initial dose of gluten, and continuing throughout the trial until the last Follow-up Visit.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Subjects must abstain from significant alcohol use throughout the trial. Significant alcohol use is defined as >1 drink/day, equal to 12 oz. beer, 5 oz. wine, or 1.5 oz. liquor.

Subjects must fast for at least 8 hours before endoscopy, CCI [redacted]. Otherwise, subjects will continue their normal GFD throughout the duration of the trial, with the addition of trial gluten.

7.4.2 Activity

Subjects will be instructed to avoid unaccustomed strenuous physical activity for 24 hours after endoscopy.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects should be discontinued or withdrawn from the trial in the event of any of the following:

1. Any clinical features of CeD are reported to be of a serious nature (Section 10.1.1).
2. The subject experiences an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
3. Confirmed pregnancy as evidenced by a positive pregnancy test.
4. Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, or continued participation poses an unacceptable risk to the subject's health.

5. Lost to follow-up. The subject did not return to the clinic, and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
6. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the electronic case report form (eCRF).
7. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal because of an AE should not be recorded in the "voluntary withdrawal" category).
8. Trial termination. The sponsor or regulatory agency terminates the trial.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the trial. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

7.7 Subject Replacement

Subjects who withdraw or are withdrawn from the trial, or who have severe villus atrophy on initial duodenal biopsy, may be replaced in order to have 6 subjects completing each group. The trial site should contact the sponsor for the replacement of subject's treatment assignment and allocation number.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

8.1 Clinical Trial Treatment

Details regarding the composition and extemporaneous preparation of the gluten packets are found in trial site procedural documents and/or similar documents. Clinical trial gluten will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted before dosing.

8.1.1 Clinical Trial Treatment Labeling

Clinical trial gluten packaging will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Trial Treatment Inventory and Storage

Clinical trial treatment material must be stored in a secure, limited-access location under the storage conditions specified on the label. Inventory (receipt and dispensing) of trial treatment must be recorded by an authorized person at the trial site.

8.1.3 Clinical Trial Treatment Blinding

This is a double-blind study; therefore, the subject, the trial site personnel, and the sponsor's staff who are involved in the treatment or clinical evaluation are blinded to treatment or intervention. Certain sponsor staff not directly involved with the treatment or evaluation may be unblinded to the treatment or intervention.

Gluten will be prepared by the trial site. The investigator will receive blind information on the subject's gluten doses in the form of sealed envelopes that will reveal the subject's trial treatment if opened. The site-designated trial personnel will maintain the gluten dose blind information. During regularly scheduled monitoring visits, a trial monitor from the sponsor or a designee will perform an inventory of all trial treatment unassigned and assigned treatment packages, sealed envelopes, and/or tear-off labels. All treatment packages will be reconciled and returned to the sponsor or a designee before trial closure.

The gluten dosage level blind is maintained through a randomization schedule held by designated personnel.

8.1.4 Randomization Code Creation and Storage

Subjects will be assigned a unique randomization sequence number and the appropriate amount of gluten for their cohort treatment group according to the randomization schedule generated by the sponsor's randomization personnel or designee. Subject randomization will be in blocks and stratified by site. All randomization information will be stored in a secure area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

A designated, unblinded qualified staff member not directly involved in the treatment or clinical evaluation can unblind a subject.

8.1.6 Ancillary Supplies

All ancillary supplies will be provided by the site, the sponsor, or a sponsor-designated contract research organization (CRO), based upon availability. If provided by the sponsor or a CRO, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or a designee.

9.0 TRIAL PROCEDURES

The following sections describe the trial procedures and data to be collected as indicated in the Schedule of Trial Procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator. For information regarding procedures that are scheduled concurrently, see Section 6.3.4.

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained before the subject enters into the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Section 13.2.

In the case where subjects have screening assessments performed before the trial, the data from the general/site screening could be included/used in the trial for those who were enrolled, as long as the procedure was performed within the protocol screening/enrollment window. A generic site screening form may be used.

9.1.2 Inclusion and Exclusion Criteria

Each subject is to be assessed according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History and Demography

Qualified site personnel are to collect significant medical history and demographic information from each subject (past and ongoing) per the site's standard of care and appropriate clinical judgment.

9.1.4 Prior and Concomitant Medications

Medications are defined as prescription and over-the-counter drugs, vitamin supplements, nutraceuticals, and oral herbal preparations. Qualified site personnel are to conduct ongoing review of medication use during the trial.

9.1.5 Assignment of Screening Numbers

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before allocation. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event.

9.2 Trial Treatment Assignment and Administration

9.2.1 Assignment to Treatment

Eligible subjects will be randomly assigned to treatment with high or low dose gluten in a 1:1 fashion.

9.2.2 Gluten Administration

CCI

[redacted]

9.3 Clinical Procedures and Assessments

Unless otherwise specified, procedures should be performed as close to the day indicated as possible.

9.3.1 Physical Examination

Qualified site personnel will conduct physical examinations.

9.3.2 Vital Sign Measurements

Subjects should rest in a semirecumbent position for at least 5 minutes before having vital sign measurements obtained. The same method (eg, same and appropriately sized cuff, manual, or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

9.3.2.1 Heart Rate and Blood Pressure

Heart rate and systolic and diastolic blood pressure will be assessed according to the clinical site's standard procedure.

9.3.2.2 Respiratory Rate and Temperature

Respiratory rate will be assessed according to the clinical site's standard procedure. Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (eg, oral or tympanic) must be used for all subsequent measurements for each individual subject and should be the same for all subjects.

9.3.2.3 Height

Height will be obtained with the subject's shoes off and jacket or coat removed.

9.3.2.4 Weight

Body weight will be obtained with the subject's shoes off and jacket or coat removed.

9.3.2.5 BMI

BMI equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). This measurement will be rounded to the nearest whole number according to the standard convention of rounding down for 0.1 to 0.4 and rounding up for 0.5 to 0.9.

9.3.3 CDSD

Subjects will use the CDSD daily throughout the trial to record any symptoms. Instructional details will be provided in a procedures manual.

9.3.4 Safety Monitoring

Safety will be assessed by monitoring trial related AEs and vital signs.

AE monitoring begins after signing of informed consent. Changes in subject health status from baseline assessment to gluten administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

9.3.5 Imaging

Subjects must fast for at least 8 hours before CCI .

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9.3.6 Endoscopy and Duodenal Biopsy

Subject preparation and preprocedure testing should be completed according to established site protocols. The initial endoscopy can be performed at any time during the Run-in period weeks before the first gluten dose. The second endoscopy can occur at any time on Day 15.

Subjects must fast for at least 8 hours before endoscopy and avoid unaccustomed strenuous physical activity for 24 hours afterward.

9.4 Laboratory Procedures and Assessments

Approximately 450 mL of blood will be drawn over the course of the entire trial.

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Endoscopic procedures will be performed after a minimum 8-hour overnight fast on the days stipulated in Table 3.a.

9.4.1 Serum Chemistry

Serum chemistry evaluations will consist of the following:

Albumin	Alkaline phosphatase
Alanine aminotransferase	Aspartate aminotransferase
Blood urea nitrogen	Calcium
Bicarbonate	Chloride
Creatinine	Glucose
γ-Glutamyl transferase	Sodium
Potassium	Bilirubin (total), will be fractionated if above the upper limit of normal
Protein (total)	IgA tTG, IgA DGP, and IgG DGP serology

9.4.2 Hematology

Hematology assessments will consist of the following tests:

Erythrocytes (red blood cells)	Hemoglobin
Hematocrit	Platelets
Leukocytes (white blood cells) with absolute differential	

9.4.3 Urine

A urine drug screen will include the following tests:

- Amphetamines
- Barbiturates
- Benzodiazepines
- Buprenorphine/metabolite
- Cannabinoids
- Cocaine/metabolites
- 3,4-methylenedioxy-methamphetamine (MDMA)
- Methadone/metabolite
- Opiates
- Oxycodone/oxymorphone
- Phencyclidine

9.4.4 Pregnancy Testing

Women of childbearing potential will undergo pregnancy testing during Screening. An additional test will be conducted on Trial Day -6 if it has been more than 7 days since the last pregnancy test.

9.5 Biomarker Samples

Histological assessments will be performed on biopsied tissue. Table 9.a provides collection parameters for primary specimens.

Table 9.a Primary Specimen Collections

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
Fresh duodenum tissue biopsy	Fresh duodenum tissue	FFPE Block FFPE Slides	DNA RNA	Biomarker measurements	Mandatory
Frozen duodenum tissue biopsy	Frozen duodenum tissue			Biomarker measurements	Mandatory
CCI					

9.5.1 Confinement

Subjects will report to the trial site as specified in Table 3.a. No overnight confinement is planned.

On Day 1, subjects will need to be available for blood collection 4 hours after receiving the first dose of gluten.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a trial; it does not necessarily have to have a causal relationship with the treatment (eg, gluten challenge).

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a treatment, whether or not it is considered related to the treatment. Anticipated symptoms related to gluten exposure that do not meet serious criteria are not considered to be AEs.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of trial treatment or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or electrocardiogram [ECG] findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, x-ray) should NOT be recorded as an AE unless related to

a trial procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of trial treatment or after any change in trial treatment, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in trial treatment, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

10.1.1 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject 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.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (Section 10.2.8.3).

10.1.2 Special Interest AEs

Not applicable.

10.1.3 Anticipated AEs

While AEs are anticipated to occur due to the underlying disease, gluten challenge, use of the CCI [redacted], or use of CCI [redacted] in the population studied under this protocol, this information does not waive the investigator's obligation to report all SAEs (including anticipated SAEs) as described in Section 10.2.8.3. AEs that may be anticipated include the following:

- Signs and/or symptoms of CeD, including gastrointestinal symptoms not described in the CDSD and extraintestinal manifestations such as skin rash, neurological/neurocognitive manifestations, elevation in liver function tests, and joint pain. Note: symptoms collected through the CDSD, including diarrhea, constipation, bowel movement frequency, abdominal pain, bloating, nausea, and fatigue should not be reported as AEs unless these events become serious.
- Risks associated with the CCI [redacted] retention and aspiration (if applicable) and any additional complications associated with medical, endoscopic, or surgical intervention necessary to address such complications (reference information provided in the study procedures manual).

- Complications associated with devices or procedures of endoscopy, intestinal biopsy, and procedural sedation. Refer to local clinical guidelines for information on these complications.
- Risks associated with the use of the CCI device or procedure of as per reference information (study procedures manual)

These anticipated AEs reflect the natural history of CeD, the response of patients with CeD to gluten challenge, and the use of devices or procedures as they are known at the time of issuance of this protocol and may change with accumulation of additional data. Any changes to anticipated AEs will be communicated to the relevant stakeholders as per regulatory requirements.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to trial treatment will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a trial treatment (including the course after withdrawal of the treatment), or for which a causal relationship is at least a reasonable possibility, that is, the relationship cannot be ruled out, although factors other than the treatment, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a treatment and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Pattern of AEs (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Trial Treatment

- Treatment withdrawn: a trial treatment is stopped because of the particular AE.
- Dose not changed: the particular AE did not require stopping a trial treatment.
- Unknown: only to be used if it has not been possible to determine what action has been taken.
- Not applicable: a trial treatment was stopped for a reason other than the particular AE eg, the trial has been terminated, the subject died, dosing with trial treatment had not yet started, or dosing with trial treatment was already stopped before the onset of the AE.
- Dose reduced: the dose was reduced because of the particular AE.
- Treatment interrupted: the dose was interrupted because of the particular AE.

10.2.7 Outcome

- Recovered/resolved: subject returned to first assessment status with respect to the AE.
- Recovering/resolving: the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved: there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed trial period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae: the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: an AE that is considered as the cause of death.

- Unknown: the course of the AE cannot be followed up because of hospital change or residence change at the end of the subject's participation in the trial.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal Liver Function Tests

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, special interest AEs, and abnormal liver function tests) will commence at the time the subject signs the informed consent. The time of AE collection should be recorded. Routine collection of AEs will continue until the last follow-up visit or phone call, approximately 30 days after the last dose of gluten. For subjects who discontinue before the administration of trial treatment, AEs will be followed until the subject discontinues trial participation.

10.2.8.2 Reporting AEs

At each trial visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the trial. Subjects experiencing an SAE before the first exposure to gluten must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin before the first exposure to gluten, whether related or unrelated to the trial procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the trial treatment or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the trial treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/intensity.
- Causality (the investigator's opinion of the causal relationship between the event and administration of trial treatment).
- Action taken with trial treatment.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

The sponsor's SAE form must be completed in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the trial treatment.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to trial participation.

Reporting of SAEs that begin before first administration of gluten will follow the same procedure for SAEs occurring on treatment.

SAE Follow-up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting Special Interest AEs

There are no specific additional reporting requirements for AEs of special interest.

10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The

sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A targeted data review will be conducted before database lock. This review will assess the accuracy and completeness of the trial database, subject evaluability, or appropriateness of the planned statistical methods.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety set will consist of all subjects who are enrolled and receive at least 1 dose of gluten. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

11.1.1.2 Biomarker Analysis Set

All subjects who complete the gluten challenge and have all the Vh:Cd measures taken.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects. Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables (eg, age, weight, and BMI), and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristic data will be provided in the data listings.

11.1.3 Safety Analysis

The safety set will be used for all summaries of safety parameters. These summaries will be presented by individual treatment group and the safety set overall.

11.1.3.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) with onset occurring within 30 days (onset date minus last date of dose +1≤30) after the last dose of gluten treatment will be included in the summary tables. All AEs will be in the listings. TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and trial treatment-related AEs, relationship of AEs to gluten treatment (related vs not related), severity of AEs, and related SAEs. Data listings will be provided for all AEs including TEAEs, AEs leading to discontinuation of gluten treatment, and SAEs. AE collection will include the time at which events were reported to clinic personnel.

11.1.3.2 Clinical Laboratory Evaluation

Not applicable; routine laboratory evaluations will be conducted only for the purpose of screening and enrolling subjects.

11.1.3.3 Vital Signs

Baseline, postdose, and changes from Baseline in vital sign measurements will be summarized. All vital sign data will be provided in the data listings.

11.1.3.4 Other Safety Parameters

Not applicable.

11.1.4 Analysis of Gluten Challenge

The gluten challenge analysis will be performed in 2 stages. First, a 2-sided paired t-test will compare Vh:Cd before and after gluten challenge to confirm a response to gluten. If a histological difference is present, then T cell markers will be evaluated with tetramers. Previous work [6] estimates ΔVh:Cd14 = -1.03 (0.96) (this is the change in Vh:Cd after a 14-day gluten challenge). Data from a recently published trial [24] estimates Δlog(Tetramer)6 = 1.87 (1.39) (this is the change in tetramer binding 6 days into a gluten challenge). These estimates will be used to calculate power and stopping thresholds.

11.1.4.1 Interim Analysis and Criteria for Early Termination

An interim analysis will be performed on 12 subjects (6 subjects at each gluten dose level). First, a 2-sided paired t-test will compare Vh:Cd before and after gluten challenge. If the absolute value of the t-statistic exceeds 2.63 (nominal p-value of 2.3%, 84% power to achieve this), indicating a change in histology was detected, then secondary endpoint functional T-cell markers (tetramers) will be evaluated with a 2-sided paired t-test. If the magnitude of this t-test is greater than 2.80 (nominal p-value of 1.7%, 95% power), then the trial will be stopped because a biomarker signal was detected. There is an 80% probability of stopping the trial at this interim analysis because of detecting a new biomarker signal.

If it is determined that more subjects are needed, a 2-sample t-test comparing the 2 dosage groups will be performed.

- If that test is significant at the 5% level (ie, the magnitude of the t-statistic exceeds 2.20), then 8 additional subjects may be enrolled into the gluten treatment group with the larger change in Vh:Cd.
- If that test is not significant, then 4 additional subjects may be enrolled into each group.

If the difference in Vh:Cd in the interim analysis was not significant, then a final 2-sided pairwise t-test will be performed, where the magnitude of the t-statistic must exceed 2.26 (nominal p-value of 3.4%, overall power >99%).

If a change in histology is detected in either the interim or final analysis, then a 2-sided paired t-test will be performed on the T cell markers. To achieve significance, the magnitude of the t-statistic must exceed 2.19 (nominal p-value of 3.9%, overall probability of tetramer significance of >99%). This design has an overall significance level of 5% for detecting a change in histology, and a separate significance level of 5% for detecting a change in T cell markers.

11.2 Determination of Sample Size

The sample size for this trial reflects several constraints. Despite having the primary analysis pooled across the 2 treatment arms, having the arms balanced is preferable so there must be an even number of subjects overall. The number of subjects was selected to detect a change in Vh:Cd in the interim analysis with 80% probability and at the final analysis with >99% probability. Additionally, it was selected to allow accurate estimation of the coefficient of variation for the secondary and exploratory endpoints, as well as to allow for comparing the 2 dosage groups.

Using the published estimates of ΔVh:Cd14 and Δlog(Tetramer)6, a single analysis with 12 subjects has 92% power to detect a change in Vh:Cd before and after gluten challenge, and a 99% power to detect a change in T-cell marker tetramer binding. With the current group sequential design, then the interim analysis has 84% power of detecting a change in histology and an independent 95% power of detecting a change in T cell markers, for an overall power of 80% to detect both. There is 99% power to detect changes in both by the final analysis.

Uncertainty in the estimates of these 2 markers may lead to questioning the accuracy of these measurements. If it is assumed that the SD of ΔVh:Cd14 and Δlog(Tetramer)6 is 50% greater than is reported in the literature, the power of this trial would be decreased. In this scenario, the trial has a 47% power to detect a histological change in the interim analysis and 89% power to detect a histological change overall. In addition, the probability of detecting a change in T cell markers is 63% at the interim analysis and 98% by the final analysis.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and trial site guarantee access to source documents by the sponsor or its designee and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, gluten, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary trial assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all trial documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before shipment of the sponsor-supplied treatment or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. Until the site receives notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The ICF and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the trial, and (2) decide whether or not to participate in the trial. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the trial, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the trial. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports and original images. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the trial. During and after the trial, only the sponsor may make trial information available to other trial investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical trial site agreement, any public disclosure (including publicly accessible websites) related to the protocol or trial results, other than trial recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the trial (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, the sponsor will, at a minimum, register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of trial, as defined in the sponsor's policies and/or standards. The sponsor's contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, the sponsor will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Trial Results Disclosure

The sponsor will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by the sponsor's policy and/or standards, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical trial insurance against the risk of injury to trial subjects. Refer to the trial site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Trial Contact Information

Contact Type/Role	Contact
SAE and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052 or Email: PVSafetyAmericas@tpna.com

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the trial site agreement.
- Responsibilities of the investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

14.1.3 Trial-Related Responsibilities

The sponsor will perform all trial-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific trial-related activities will perform these activities in full or in partnership with the sponsor.

14.1.4 List of Abbreviations

AE	adverse event
APC	antigen-presenting cells
BMI	body mass index
CDSD	celiac disease symptom diary
CeD	celiac disease
CFR	Code of Federal Regulations
CRO	contract research organization
DGP	anti-deamidated gliadin peptide
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin block
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFD	gluten-free diet
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	institutional ethics committee
IEL	intraepithelial lymphocyte
IHC	immunohistochemistry
INF-γ	interferon-γ
IRB	institutional review board
mRNA	messenger RNA
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
CCI	[redacted]
CCI	[redacted]
PT	preferred term
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TCR	T cell receptor
TEAE	treatment-emergent adverse event
tTG	anti-tissue transglutaminase
CCI	[redacted]
Vh:Cd	villus height to crypt depth ratio

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this trial to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical trial database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

The eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of treatment disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on

degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this trial.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that trial related procedures, including trial specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
6. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or

that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied trial treatment, and return all unused sponsor-supplied treatment to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
17. The anticipated expenses, if any, to the subject for participating in the trial.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
22. A statement that results of biomarker analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) the sponsor, its affiliates, and licensing partners; (2) business partners assisting the sponsor, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, the sponsor will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to the sponsor's research databases for purposes of developing a better understanding of the safety of the trial treatment, studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that trial results are published.
25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active with a nonsterilized male partner must use effective contraception (as

defined in the informed consent) from signing the informed consent and throughout the duration of the trial, and for 3 months after the conclusion of trial participation.

26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

The sponsor will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- The sponsor, its affiliates, and licensing partners.
- Business partners assisting the sponsor, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by the sponsor and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the trial and/or other clinical studies.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to medications used in other clinical studies.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within sponsor, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details, and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by the sponsor and other parties for the purposes described above.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Quality Assurance Approval	09-Oct-2017 14:24 UTC
	Nonclinical Scientist Approval	09-Oct-2017 14:56 UTC
	Clinical VP Approval	09-Oct-2017 16:18 UTC
	Biostatistics Approval	11-Oct-2017 01:08 UTC