TAKEDA PHARMACEUTICALS

PROTOCOL

Long Title:	**A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose-Ranging Study to Evaluate the Efficacy and Safety of TAK-101 for the Prevention of Gluten-Specific T Cell Activation in Subjects with Celiac Disease on a Gluten-Free Diet**		
Short Title:	**Dose-Ranging Study of the Efficacy and Safety of TAK-101 for Prevention of Gluten-Specific T Cell Activation in Subjects with Celiac Disease on a Gluten-Free Diet**		
Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue, Lexington, MA 02421		
Study Number:	TAK-101-2001		
IND Number:	017579	**EudraCT Number:**	Not Applicable
Compound:	TAK-101 (TIMP-GLIA)		
Date:	11 June 2020	**Version/Amendment Number:**	Initial version

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center Americas–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America Contact
Serious adverse event and pregnancy reporting	United States and Canada: Email: PVSafetyAmericas@tpna.com Fax: +1-224 554-1052
Medical Monitor (medical advice on protocol and study drug)	IQVIA Medical Monitor (Refer to the contact information list)
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Daniel Leffler, MD, MS, AGAF Medical Director, Clinical Science Office Telephone: +1 6176797323 Mobile: +1 7816085918

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

Daniel Leffler, MD, MS, AGAF Medical Director, Clinical Science	Date	Pengyu (Tina) Liu. PhD Scientific Fellow, Statistical and Quantitative Sciences	Date

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator. (Appendix B)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

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2.0 STUDY SUMMARY

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TAK-101</td></tr>
<tr><td>Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose-Ranging Study to Evaluate the Efficacy and Safety of TAK-101 for the Prevention of Gluten-Specific T Cell Activation in Subjects with Celiac Disease on a Gluten-Free Diet</td><td>IND No.: 017579</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Number: TAK-101-2001</td><td colspan="2">Phase: 2</td></tr>
<tr><td colspan="3">Study Design:
This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of TAK-101 for prevention of gluten-specific T cell activation in adult subjects with celiac disease (CeD) on a gluten-free diet (GFD). Two study cohorts are planned for the study, the second of which may include 1 or 2 dose levels, depending on safety, tolerability, and activity observed in the first cohort. A total of approximately 108 subjects with well controlled CeD on a GFD for at least 6 months are planned to be enrolled. Eligible subjects will receive 2 intravenous (IV) infusions of TAK-101 and/or placebo, each separated by 7 days (on Days 1 and 8). Approximately 45 subjects will be randomly assigned initially into 1 of 3 treatment groups with 1:2:2 randomization ratio in the first study cohort:
• Two infusions of placebo.
• One infusion of 2 mg/kg TAK-101 followed by 1 infusion of placebo.
• Two infusions of 2 mg/kg TAK-101.
A decision will be made to stop the study or continue into the second study cohort of the study by the sponsor safety management team (SMT), taking into account the recommendations of the independent data monitoring committee (DMC). Up to approximately 63 subjects will be randomized into the second cohort.
If it is deemed appropriate to open the second cohort at the TAK-101 4 mg/kg dose level:
The first 22 subjects of the second cohort will be randomly assigned to 1 of 3 treatment groups with 1:2:2 randomization ratio:
• Two infusions of placebo.
• One infusion of 4 mg/kg TAK-101 followed by 1 infusion of placebo.
• Two infusions of 4 mg/kg TAK-101.
In parallel, the Day 20 change from baseline in interferon-gamma (IFN-γ) spot forming units (SFUs) from all subjects in the first cohort will be reviewed by the DMC (unblinded data) and SMT (blinded data), and a decision will be made as to whether a 1 mg/kg treatment arm should be tested.
If the first 22 subjects in the second cohort have been enrolled before this decision is made, then further enrollment will be paused.
If the 1 mg/kg treatment arm is not needed, the remaining 23 subjects will continue to be enrolled into the second cohort and randomly assigned to 1 of 3 treatment groups listed above, with 1:2:2 randomization ratio (there will be a total of 45 subjects in the second cohort). If, however, the 1 mg/kg treatment arm is needed, the remaining 41 subjects will be randomly assigned to 1 of 4 treatment groups with 1:2:2:4 randomization ratio (there will therefore be a total of 63 subjects in the second cohort):
• Two infusions of placebo.
• One infusion of 4 mg/kg TAK-101 followed by 1 infusion of placebo.
• Two infusions of 4 mg/kg TAK-101.
• Two infusions of 1 mg/kg TAK-101.
If it is decided not to open the second cohort at the 4 mg/kg dose level:</td></tr>
</table>

In the event that a decision is made not to proceed to the 4 mg/kg dose level, the Day 20 change from baseline in IFN-γ SFUs from all subjects in the first cohort will be reviewed by the DMC (unblinded data) and the SMT (blinded data), and a decision will be made as to whether to evaluate the 1 mg/kg dose level.

- If 1 mg/kg is recommended to be tested, the second cohort will consist of 45 subjects randomly assigned to 1 of 3 treatment groups with 1:2:2 randomization ratio:
  - Two infusions of placebo.
  - One infusion of 1 mg/kg TAK-101 followed by 1 infusion of placebo.
  - Two infusions of 1 mg/kg TAK-101.
- If 1 mg/kg is not recommended to be tested, the study will terminate enrollment.

Subjects aged 18 to 75 years, inclusive, with documented history of biopsy-proven confirmed CeD, which is well-controlled and on a GFD for a minimum of 6 months will be screened. Eligible subjects who meet all inclusion and no exclusion criteria and provide written informed consent will undergo a single-day 3 g oral gluten challenge approximately 4 weeks before randomization (run-in gluten challenge). Participation in the run-in gluten challenge is a requirement of study participation; however, symptomatic or biomarker response to the run-in gluten challenge will not inform eligibility for randomization. Randomized subjects will receive 2 IV infusions of TAK-101 and/or placebo, each separated by 7 days (on Days 1 and 8). Subjects will be randomly assigned to receive placebo and/or TAK-101 at doses of 2 mg/kg in the first study cohort. In the second study cohort, subjects will be randomly assigned to receive placebo or TAK-101 at a dose of either 4 mg/kg or 1 mg/kg. For both study cohorts, the maximum dose of TAK-101 will be 500 mg per dose. Randomization will be stratified based on HLA type into 3 strata:

1. HLA DQ2/DQ2, DQ2/B1*02, DQ2/DQ8
2. HLA DQ2/x, B1*02/B1*02, DQ8/B1*02
3. HLA DQ8/DQ8, DQ8/x

On Days 15 through 20, subjects will undergo a 6-day gluten challenge by consuming 12 g of gluten daily for 3 days, followed by 6 g of gluten daily for 3 days. Subjects will subsequently undergo single-day 3 g gluten challenges at Weeks 8, 14, and 20. Other than the gluten challenges, subjects will continue to follow a GFD throughout the study.

Subjects will be observed for adverse events (AEs), including infusion reactions (IR) and cytokine release syndrome (CRS), for up to 2 hours following infusion on Days 1 and 8. Subjects will be assessed regularly for safety and tolerability by AEs, physical examination, vital signs, and routine clinical laboratory tests (chemistry, liver tests, and hematology).

Sampling for immunogenicity (antidrug antibodies [ADA] assay, deamidated gliadin peptide [DGP]-immunoglobulin G [IgG] assay), drug-induced cytokine release syndrome, safety laboratory tests for complement levels (C3a, C5a, and SC5b-9), liver tests, analysis of gliadin-specific T cells, blood cell immunophenotyping, and pharmacokinetic (PK) evaluation will be collected as specified in the Schedule of Study Procedures.

Sites will employ all efforts to see subjects as described in the clinical assessments. In unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. These data collected with alternative methods may be handled differently in the final data analysis. This will be documented in the statistical analysis plan.

The database will be locked when all subjects have completed the study or discontinued the study early. After final database lock, the study will be unblinded and a clinical study report will be prepared.

Primary Objectives:

To compare the number of baseline IFN-γ SFUs to the number of IFN-γ SFUs after a 6-day oral gluten challenge among subjects treated with TAK-101 versus placebo.

Secondary Objectives:

- Evaluate the safety of various dose levels of TAK-101.
- Evaluate gluten-induced CeD symptoms in subjects treated with TAK-101 versus placebo.
- Evaluate change from baseline in gliadin-specific T cell activation following an oral gluten challenge in subjects treated with TAK-101 or placebo.
- Characterize the durability of TAK-101 based on gluten challenge–induced plasma interleukin-2 (IL-2).
- Characterize the PK of TAK-101.
- Characterize the dose-response relationship of TAK-101 in subjects with CeD on a GFD.
- Assess the immunogenicity of various dose levels of TAK-101.

Subject Population: Subjects aged 18 to 75 years, inclusive, who are HLA-DQ2 and/or HLA-DQ8 positive with biopsy-confirmed CeD and on a GFD for ≥6 months.

Number of Subjects:	**Number of Sites:**
Estimated total: Approximately 108 subjects randomized (22 to each treatment arm).	Estimated total: 34 sites in the United States and Canada.
Dose Level(s): Cohort 1: Placebo: 2 doses, 1 week apart. TAK-101 2 mg/kg: 1 dose; placebo: 1 dose, 1 week apart. TAK-101 2 mg/kg: 2 doses, 1 week apart. Cohort 2 (subject to review of Cohort 1 data): Placebo: 2 doses, 1 week apart. TAK-101 4 mg/kg: 1 dose; placebo: 1 dose, 1 week apart. TAK-101 4 mg/kg: 2 doses, 1 week apart.TAK-101 1 mg/kg: 2 doses, 1 week apart. TAK-101 1 mg/kg: 1 dose; placebo: 1 dose, 1 week apart.	**Route of Administration:** IV infusion over ~2.5 hours
Duration of Treatment:	**Period of Evaluation:**
20 weeks (initial treatment to final gluten challenge)	Up to 26 weeks

Main Criteria for Inclusion:

- Biopsy-confirmed CeD that is well-controlled, defined as mild or with no ongoing signs or symptoms felt to be related to active CeD and with immunoglobulin A (IgA) tissue transglutaminase <2 × upper limit of normal (ULN) and IgG DGP <3 × ULN.
- On a GFD for ≥6 months.
- HLA-DQ2 and/or HLA-DQ8 positive during screening laboratory testing.

Main Criteria for Exclusion:

- Known inflammatory gastrointestinal disorders or autoimmune diseases, other than well-controlled autoimmune thyroid disease or well-controlled type 1 diabetes mellitus (defined as glycosylated hemoglobin <8 and no hospitalization in the last 12 months for hyper/hypoglycemia).
- Known or suspected refractory CeD or ulcerative jejunitis.
- Additional food allergies or intolerances that prevent participation in the food challenge.
- Ongoing systemic immunosuppressant, systemic corticosteroid treatment, or treatment with systemic immunosuppressants or corticosteroids in the 12 weeks before run-in gluten challenge.
  - Immunosuppressive doses of corticosteroids: more than 3 mg/day budesonide for more than 1 week within 3 months before Dose 1, more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more within 6 months before Dose 1, any dose of oral or IV corticosteroids within 30 days of Day 1, or high dose inhaled corticosteroids (>960 μg/day of beclomethasone dipropionate or equivalent), or other immunosuppressive agents.
- Known or suspected chronic liver disease or positive for hepatitis B or C. For hepatitis B or C, the subject has 1 of the following at screening:
  - Chronic hepatitis B virus infection defined as being positive for hepatitis B surface antigen or hepatitis B core antibody, or
  - Chronic hepatitis C virus (HCV) infection defined as positive for HCV antibody that is confirmed with a positive HCV RNA viral load test (those treated and cured for HCV infection are allowed).
- Alanine aminotransferase or aspartate aminotransferase >1 × ULN, or total bilirubin >1 × ULN.
- Known or suspected COVID-19 by the investigator within the past 2 months (additional testing may be performed at the discretion of the investigator). Positive antibody testing for COVID-19 without other evidence of current or recent active infection does not exclude participation.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

Change from baseline (Day 15, or Day 1 in the absence of Day 15) to Day 20 in IFN-γ SFUs based on results of a gliadin-specific enzyme-linked immunospot (ELISpot) assay.

Secondary Endpoints:

- Safety and tolerability as assessed by AEs, IRs, CRS, physical examinations, vital signs, and clinical laboratory testing, including liver tests.
- Change in Celiac Disease Symptom Diary version 2.1 (Celiac Disease Symptom Diary [CDSD] v2.1; 24-Hour Recall) 3-day average score from Day 1 to post-gluten challenge on Day 20, and Weeks 8, 14, and 20 (Postbaseline 3-day average score is counted from the initiation of gluten challenge, Day 1 3-day average score is the average of most recent 3 days before the first dose of study treatment).
- Change in CDSD v2.1 (24-Hour Recall) 3-day peak score from baseline to post-gluten challenge on Day 20, Week 8, 14 and 20. (Peak score is the highest score in the 3 days following gluten challenge starting on the initiation of gluten challenge for challenges at Weeks 8, 14, and 20 and the highest score during and the 3 days following the Day 15-20 gluten challenge.) Baseline value will be measured on Day 1.
- Change from pre- to 4 hours post-gluten challenge in plasma IL-2.
- Plasma concentration of TAK-101 after the first and second dose.
- Change in serum concentration of ADAs to TAK-101 (DGP-IgG) from baseline (before TAK-101 administration).

Statistical Considerations:

Analysis Sets:

The full analysis set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postbaseline measurements. Subjects will be analyzed according to the treatment they were

randomized to receive.

The safety analysis set will consist of all subjects who received at least 1 dose of study drug. Subjects will be analyzed according to actual treatment received.

The biomarker analysis set will consist of all subjects who have baseline and Day 20 ELISpot assay results.

The PK analysis set is defined as all randomized subjects who received at least 1 dose of study drug and for whom there is at least 1 reported PK concentration.

Efficacy Analysis:

Efficacy analyses for the ELISpot will be analyzed using the biomarker analysis set. All other efficacy analyses will be based on the FAS. All statistical hypothesis testing will be 2-sided and conducted at the 0.05 significance level.

Primary Efficacy Analysis: The primary endpoint (change from baseline to Day 20 in IFN-γ SFUs) will be compared between each TAK-101 arm and the placebo arm using the Wilcoxon rank-sum test based on the biomarker analysis set. The Hodges-Lehmann estimator of location shift and the associated 95% CI will be used to estimate the treatment difference between each TAK-101 dose arm and placebo. Descriptive statistics will also be used to summarize the primary efficacy endpoint.

Multiplicity will be adjusted using the fixed-sequence testing procedure to compare each treatment arm with the placebo arm. All tests will be performed at the 0.05 level in the sequence below. If any hypothesis test in this sequence is not significant, all subsequent tests will not be performed; however, p-values will still be presented and are regarded as descriptive.

1. TAK-101 4 mg/kg 2 infusions versus placebo.
2. TAK-101 4 mg/kg 1 infusion versus placebo.
3. TAK-101 2 mg/kg 2 infusions versus placebo.
4. TAK-101 2 mg/kg 1 infusion versus placebo.
5. TAK-101 1 mg/kg 2 infusions versus placebo.
6. TAK-101 1 mg/kg 1 infusion versus placebo.

If any treatment group is not opened or terminated early, hypothesis testing of the treatment group will not be performed and analysis will proceed with the next dose tested in the fixed-sequence testing specified above.

Secondary Efficacy Analyses: Continuous endpoints measured at a single timepoint (change in CDSD v2.1 [24-Hour Recall] 3-day average score from baseline to Day 20; change in CDSD v2.1 [24-Hour Recall] peak score from baseline to Day 20; and pre- to 4 hours post 12 g gluten challenge change in IL-2 at Day 15) will be analyzed using an analysis of covariance model. The continuous longitudinal endpoints (change in CDSD v2.1 [24-Hour Recall] 3-day average score from baseline to Weeks 8, 14, and 20; change in CDSD v2.1 [24-Hour Recall] peak score from baseline to Weeks 8, 14, and 20; and changes from pre- to 4 hours post single-day 3 g gluten challenge in IL-2 and CDSD v2.1 [Short Recall] at Weeks 8, 14, and 20) will be analyzed using a mixed model for repeated measures with fixed effects for the treatment group, visit, treatment by visit interaction, the randomization stratification factor, and with the baseline measurement as a covariate. An unstructured (co)variance structure will be used to model the within-subject errors. The point estimates for the treatment difference from placebo and the 95% CI will be provided for the difference between each arm of TAK-101 versus placebo at each timepoint of interest.

Safety Analysis:

Safety analyses will be performed using the safety analysis set. All AEs will be coded using the Medical Dictionary for Regulatory Activities. Data will be summarized using preferred term and primary system organ class. AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Change from baseline in clinical laboratory tests and vital signs will be summarized descriptively by treatment group. Subjects with markedly abnormal values for laboratory tests and vital signs will be summarized and listed.

Sample Size Justification: The planned sample size is approximately 108 subjects based on IFN-γ ELISpot assay data (IFN-γ SFUs) seen in previous analogous CeD studies. Assuming an 80% probability that the Day 20 IFN-γ SFU change from baseline in the placebo group is greater than that of the highest dose arm of TAK-101 (ie, 2 infusions of 4 mg/kg), a sample size of 90 subjects (15 subjects per arm) will have 80% power to detect a difference in the distribution for the primary endpoint between the highest dose arm of TAK-101 and the placebo arm. The 2-sided statistical hypothesis will be tested using the Wilcoxon rank-sum test and 0.05 significance level. To account for an assumed dropout rate of 17%, approximately 108 subjects will be randomized (18 subjects per arm).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

γδ	gamma delta
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CDSD v2.1	Celiac Disease Symptom Diary version 2.1
CeD	celiac disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
DGP	deamidated gliadin peptide
DMC	data monitoring committee
DTH	delayed type hypersensitivity
ECG	electrocardiogram
eCRF	electronic case report form
ELISpot	enzyme-linked immunospot
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFD	gluten-free diet
GLP	Good Laboratory Practice
GSRS	Gastrointestinal Symptom Rating Scale
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-γ	interferon-gamma
IL-2	interleukin-2
INR	international normalized ratio
IP	investigational medicinal product
IR	infusion reaction

IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCL	Nanotechnology Characterization Laboratory
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PLGA	poly(lactic-co-glycolic acid)
PPS	per protocol set
PRO	patient-reported outcome
PTE	pretreatment event
SAE	serious adverse event
SFU	spot forming units
SMT	safety management team
SUSAR	suspected unexpected serious adverse reaction
Th1	Type 1 Helper T cells
TIMP	tolerogenic immune modifying nanoparticles
tTG	tissue transglutaminase
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vh:Cd	villus height to crypt depth ratio

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Background

Celiac disease (CeD) is a multi-system autoimmune disease triggered by ingestion of dietary gluten in genetically susceptible individuals [1]. Gluten-related polypeptides from wheat (gliadin), rye (secalin), and barley (hordein) are enriched in glutamine/prolamine, and as a result, they are incompletely digested by peptidases, allowing them to cross into the small intestinal submucosa [2]. These ~10-mer to 40-mer peptides are selectively deamidated by the endogenous enzyme tissue transglutaminase (tTG) type 2, which normally is involved in wound repair and collagen cross-linking. These negatively charged peptides can then bind with high affinity to HLA-DQ2/DQ8 on antigen presenting cells which elicits both an antigen specific CD4+ T cell response and a non–gluten-specific CD8+ T cell response. It is thought that the CD8+ T cells in the blood traffic to the small intestine and comprise the majority of the intraepithelial lymphocytes responsible for epithelial cell destruction [3]. The tissue proinflammatory response includes interferon-gamma (IFN-γ) release along with the release of metalloproteinases and other tissue damaging mediators [4,5]. Intestinal injury is characterized by villous atrophy, crypt hyperplasia, and infiltration of lymphoid cells in both the epithelium and lamina propria. Antibody-mediated inflammation, such as IgA anti-transglutaminase 2 autoantibodies, is thought to drive extra-intestinal manifestations, such as dermatitis herpetiformis [6]. Recent population-based studies in the United States (US) indicate that the serologic prevalence of CeD is 1.1% (95% CI, 1.0%-1.2%) [7] and approximately 0.5% globally [8].

Currently the only option for patients with CeD is a gluten-free diet (GFD) which involves strict, lifelong avoidance of exposure to >20 ppm proteins from wheat, barley, and rye (fao.org/fao-who-codexalimentarius/codex-texts/list-standards/en/, Codex Alimentarius Standard for Foods for Special Dietary Use for Persons Intolerant to Gluten, Codex Stan 118-1979, Accessed 15 May 2020). The threshold of daily gluten that will cause mucosal injury in both adults and children is thought to be 10 to 50 mg per day – or about 1/100th of a slice of bread [9,10]. The GFD is not felt to be sufficient for all patients as diet modification does not result in disease control in approximately 25% of patients and the vigilance needed to maintain strict gluten avoidance places a high degree of burden on patients and caregivers. There is known to be a high degree of variability in sensitivity to gluten exposure between patients, with some patients developing severe symptoms and small intestinal mucosal injury with minimal gluten exposure, and other patients who require large amounts of gluten over weeks or even months before a measurable immune reaction is triggered [11,12]. The reasons for this heterogeneity in gluten sensitivity is unclear but may be related to both genetic predisposition and microbiome influences [13,14]. While many patients can attain sufficient disease control with gluten avoidance practices, a subset of patients are sufficiently sensitive that attainable gluten avoidance does not result in CeD remission and patients suffer from ongoing symptoms and intestinal injury which increases the risk of long-term complications including malignancy and osteoporosis [15,16].

This low threshold for gluten-induced CeD activation in a subset of patients is especially concerning given emerging data from Europe, the US and Canada that gluten exposures of ~250 to 500 mg per day are common even in well-educated and motivated patients. This has been documented by several methodologies, which may explain some variability in the estimations of frequency and amount of gluten exposure. For example, from a United Kingdom (UK) survey study, ~70% of patients reported regular symptomatic gluten exposure despite attempts at gluten avoidance [17]. New tests of gluten exposure in feces and urine from Spain and Argentina suggest that gluten exposures of >100 mg can be detected in 25% to 50% of adult and pediatric patients [18-20]. Data pooled from a multicenter study conducted in the US, Canada, Finland, Ireland, Norway, and the UK estimated that mean gluten exposure was 150 to 400 mg per day [21]. A study out of the US using a portable sensor to detect gluten in food found that gluten was detected in 32% of labeled gluten-free restaurant foods [22]. Finally, a study from Canada directly measuring gluten in reserved portions of patients with CeD meals using certified laboratory testing found that 86% of patients with CeD were exposed to gluten over a 10-day period [23].

4.1.2 Name and Description of Study Drug

TAK-101 is a first-in-class, non-immunosuppressive nanoparticle encapsulating gliadin from wheat designed to specifically induce gliadin-specific T cell tolerance, thereby reducing the underlying pathology of CeD. It is comprised of refined partially deamidated gliadin extract drug substance (~8 to 10 µg of gluten per mg of poly(lactic-co-glycolic acid) [PLGA] particles) dispersed within a negatively charged (approximately -40 mV) polymer matrix of PLGA (50:50 acid-end group) particles (400-800 nm in size). TAK-101 is reconstituted in sterile water for injection and administered by intravenous (IV) infusion.

4.1.3 Summary of Nonclinical Findings

4.1.3.1 In Vivo Pharmacology

After IV injection tolerogenic immune modifying nanoparticles (TIMP), like TAK-101, interact with antigen presenting cells via the scavenger receptor MARCO [24]. The antigen presenting cells then present gliadin peptides, in the context of major histocompatibility complex (MHC) Class II, to CD4 T cells in the spleen and liver. Antigen presentation under these conditions in mice results in tolerance. These studies with mice suggest that tolerance is the result of early anergy, with regulatory T cells playing a major role in long-term tolerance maintenance.

Primary pharmacology of TAK-101 was studied in 2 different mouse models of disease.

1. **Delayed type hypersensitivity (DTH):** The prototypical DTH reaction is caused by Type 1 Helper T cells (Th1) that are activated by antigen leading to clonal expansion and differentiation of antigen-specific cells in Th1 cells. Upon re-encounter with antigen, the antigen specific Th1 clones undergo further expansion and secretion of effector molecules, that result in a local tissue reaction which is readily measured by changes in ear swelling [24,25]. Mice treated with 2 doses of TAK-101 IV up to 125 mg/kg (human equivalent dose [HED] 10.16 mg/kg) before and after immunization showed a significant reduction in ear swelling and

reduced ex vivo splenic T cell proliferation. This model was used to determine the predicted effective dose range in humans.

2. **Adoptive transfer model:** To induce enteropathy, splenocytes from gliadin immunized C57BL/6 mice were adoptively transferred to RAG 1 -/- (recombination-activating gene) recipient mice. In this model of gluten-dependent intestinal disease, 2 infusions of 125 mg/kg (HED 10.16 mg/kg) TAK-101 showed abrogation of weight loss and a statistically significant reduction in small intestinal pathology. Reduction in disease was also reflected in the inhibition of gliadin-specific T cell activation.

Taken collectively, the in vivo pharmacology data supports the activity of TAK-101 in physiologic systems involved in CeD at the proposed human doses.

4.1.3.2 Nonclinical Safety Findings

Safety pharmacology of TAK-101 was studied in vitro and ex vivo.

In vitro and ex-vivo safety pharmacology studies were used to assess the interaction of TAK-101 with blood constituents after IV infusion, to assess TAK-101 effects on liver cells, and to assess the potential of TAK-101 administration to induce immune complex deposition in the kidney. Safety pharmacology assessments included a panel recommended by the National Cancer Institute (NCI) Nanotechnology Characterization Laboratory (NCL) which was designed specifically for the evaluation of nanoparticles being developed for clinical use (ncl.cancer.gov/resources/assay-cascade-protocols). This NCI-NCL panel included:

- Blood contact studies to evaluate TAK-101 effects on hemolytic potential, platelet aggregation, complement activation, and coagulation.
- Immune safety pharmacology studies to evaluate TAK-101 effects on maturation of dendritic cells, macrophage nitric oxide production, chemotaxis, phagocytosis, and mouse granulocyte colony forming units.
- Liver safety pharmacology studies to evaluate effects of TAK-101 on hepatocyte cytotoxicity (thiazolyl blue tetrazolium bromide and lactate dehydrogenase release) and oxidative stress (levels of glutathione, lipid peroxidation, reactive oxygen species) and apoptosis.

The results of these in vitro studies indicate that TAK-101 is biocompatible for IV infusion with no effects observed at HEDs as high as 200 mg/kg.

In addition to the NCI-NCL panel, TAK-101 was investigated in safety pharmacology studies (in vitro or ex vivo) to examine potential immunologic toxicity. The effects of TAK-101 on human T cell activation or cytokine production in peripheral blood mononuclear cells (PBMC) from healthy donors, gluten-free celiac donors, as well as active/newly diagnosed celiac donors were examined. At concentrations as high as 1.25 mg/mL (HED 100 mg/kg), TAK-101 did not cause T cell proliferation or proinflammatory cytokine production.

The ability of TAK-101 to induce type III hypersensitivity was investigated in kidney tissues from the mouse DTH and HLA-DQ8/huCD4 studies. TAK-101 did not induce type III hypersensitivity reactions in the mouse kidneys examined.

In vivo toxicology studies include an ongoing exploratory rat non-Good Laboratory Practice (GLP) single-dose study (up to 600 mg/kg [30 mg/mL]), a completed rat GLP repeat-dose study (up to 75 mg/kg [15 mg/mL]; toxicokinetic evaluation included), a completed rat non-GLP repeat-dose study (100 and 150 mg/kg [20 and 30 mg/mL, respectively]; no toxicokinetic data collected), and a completed monkey non-GLP single ascending and repeat dose study (up to 225 mg/kg [30 mg/mL]; toxicokinetic evaluation included). In these toxicology studies, TAK-101 was administered IV since this is the route intended in human clinical studies.

Non-GLP single-dose study in rats: In an exploratory non-GLP single-dose rat toxicology study to explore the effect on nanoparticle concentration, dose, and infusion time on liver effects (report pending), administration of TAK-101 as an IV infusion up to 24 hours was associated with early mortalities at ≥150 mg/kg (HED 24 mg/kg) and dose-dependent liver and platelet effects at ≥75 mg/kg (HED 12 mg/kg). Liver effects consisted of minimal to moderate sinusoidal infiltrates of macrophages and fewer lymphocytes at all doses and minimal to marked hepatocellular necrosis at ≥150 mg/kg and platelet effects consisted of minimal to marked decreases at all doses. Liver effects correlated with minimal to marked increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamate dehydrogenase, alkaline phosphatase (ALP), and total bilirubin. After a 7-day nondosing period, hepatocellular necrosis was no longer observed, but sinusoidal infiltrates were of increased severity and were often granulomatous in nature at ≥300 mg/kg (HED 48 mg/kg). Additionally, collagen deposition was present in regions of inflammation at ≥300 mg/kg. Platelet decreases had completely reversed.

GLP repeat-dose study in rats: In this study, TAK-101 was administered via IV bolus to rats at doses up to 75 mg/kg (HED 12 mg/kg) on Days 1, 8, and 15. Animals were euthanized on Day 16 or Day 43 (after a 28-day recovery period). All animals survived until the scheduled necropsy. There were no significant abnormal clinical findings during the study and no drug-related effects were noted on body weight, food consumption, ophthalmology exams, physical exams, clinical observations, functional observational battery, body temperature, serum cytokine levels, and macroscopic and microscopic examination. The no-observed-adverse-effect level (NOAEL) from this pivotal GLP toxicology study in rats was determined to be the high dose of 75 mg/kg (HED 12 mg/kg). In addition, there were no effects on the central nervous system in any of the parameters evaluated. Local tolerance was assessed in the completed toxicology studies. No injection site reactions were noted.

Non-GLP repeat-dose study in rats: In this study, TAK-101 was administered via IV bolus to rats at 100 or 150 mg/kg (HED 24 mg/kg) on Days 1 and 5. Animals were euthanized on Day 8. All animals survived until the scheduled necropsy and there were no abnormal clinical observations. Microscopic liver effects were noted at 100 and 150 mg/kg and included sinusoidal infiltrates of mononuclear cells, increased hematopoiesis, increased mitoses in hepatocytes, and biliary hyperplasia. Reversibility was not assessed.

Non-GLP single- and repeat-dose study in monkeys: In this study, TAK-101 was administered via IV infusion (2 hours) to monkeys at 3, 30, 90, and 225 mg/kg (single-dose phase) or 20 or 60 mg/kg on Days 1, 8, and 15 (repeat-dose phase). The single-dose phase was nonterminal and animals in the repeat dose phase were euthanized on Day 16 or on Day 29 after a 2-week recovery

period. In the single-dose phase, evaluation was limited to clinical findings and clinical pathology. There were no significant abnormal clinical findings. Marked increases in liver parameters (ALT, AST, glutamate dehydrogenase) and decreases in platelets were noted at 90 and 225 mg/kg (HED 29 and 73 mg/kg, respectively). These effects were reversed or reversing after a 3-day recovery period. In the repeat-dose phase, microscopic liver effects were noted at 60 mg/kg (HED 19 mg/kg) and included minimal mixed infiltrates and minimal hepatocellular degeneration/necrosis with no clinical pathology correlates. Microscopic liver findings were still present after a 14-day nondosing period.

4.1.4 Summary of Clinical Findings

Phase 1

The phase 1 program was designed to evaluate the safety and tolerability of single and multiple ascending doses of TAK-101 in subjects aged 18 to 75 with biopsy-proven CeD. Single ascending doses ranged from 0.1 to 8 mg/kg of TAK-101 (Part A); repeat doses of TAK-101 included 2, 4, and 8 mg/kg (Part B). This study assessed the safety, tolerability and pharmacokinetics (PK) of IV TAK-101 in subjects with treated CeD with resolved symptoms on a GFD. The starting dose was determined by the NOAEL in rats (which was the highest dose tested in the pivotal GLP study) and the pharmacologically active dose in mice using the DTH model. A total of 17 subjects were enrolled sequentially into Part A of the study. Two subjects each received doses of 0.1 and 0.5 mg/kg; 3 subjects each received doses of 1, 2, and 4 mg/kg; and 4 subjects received 8 mg/kg. Upon review of all safety data, an independent data monitoring committee (DMC) recommended that 1) the investigational product be diluted in 200 mL of normal saline (originally 100 mL), and 2) the investigational product be infused over approximately 2.5 hours to 20 mL/hour for the first 15 minutes, 40 mL/hour for the next 15 minutes, and then 80 mL/hour for the duration of the infusion, rather than a constant rate over 30 minutes. A total of 6 subjects were enrolled sequentially into Part B of the study; 2 subjects received 2 doses of 2 mg/kg, 2 subjects received 2 doses of 4 mg/kg, and 2 subjects received 2 doses of 8 mg/kg. No infusion-related reactions were reported in Part B of the study. The risk of infusion-related reactions was mitigated in Part B of the study by increasing the volume of solution (to reduce the concentration of TAK-101), lengthening the duration of infusion, and modifying the rate of the infusion. There were no serious adverse events (SAEs) reported in any subject in Part A or Part B. Antidrug antibodies (ADAs) were assessed through antibodies to gliadin and were unchanged from baseline in all subjects. All but 1 adverse event (AE) were Grade ≤2 (moderate); 1 subject reported Grade 3 (non-celiac) colitis that the investigator deemed not related to TAK-101. The most frequent events observed in ≥2 subjects include: flushing (n = 5, 29%), headache (n = 3, 18%), back pain (n = 3, 14%), fatigue (n = 2, 12%), abdominal pain (n = 2, 12%), and diarrhea (n = 2, 12%). Both flushing and back pain appeared to be related to increased dose. Due to these reactions, and as a dose predicted to be effective based on nonclinical models had been reached, dosing was stopped at 8 mg/kg before enrollment of the final planned dose cohort of 10 mg/kg. There was no trend in any other AE.

Phase 2a

This study assessed the ability of 2 doses of 8 mg/kg TAK-101 to prevent CeD activation during gluten challenge. The primary outcome for the study was assessment of increase from baseline in gluten-specific peripheral T cells, measured by IFN-γ spot forming units (SFUs) in a gliadin-specific enzyme-linked immunospot (ELISpot) assay after an oral gluten challenge, among subjects treated with TAK-101 or placebo. The key secondary outcome was change from baseline in small intestinal mucosal injury assessed by villus height to crypt depth ratio (Vh:Cd) following an oral gluten challenge in subjects treated with TAK-101 or placebo.

This study met its primary endpoint with a statistically and clinically significant reduction in ELISpot response in TAK-101 versus placebo-treated subjects. A total of 34 subjects were treated in the study, with 16 in TAK-101 and 18 in placebo arms. Ten of 16 placebo subjects (62.5%) had an increase in gluten responsive T cells (based on SFUs), to gluten challenge (ie, responder) compared to only 3 of 13 subjects (23.1%) treated with TAK-101. The relative rate reduction of the immune response is 63.1%.

While the study was not powered for a difference in change in small intestinal mucosal injury measured by Vh:Cd, placebo subjects demonstrated a reduction (worsening) in the Vh:Cd ratio of 0.63 compared to a reduction of 0.18 in the TAK-101 treated arm. Additional supportive data includes a significant reduction in activated (CD38+) gut homing T cells (a4b7+ and/or aEb7+) in the TAK-101 treated group compared to controls suggesting reduction of gut homing effector cells in the setting of gluten exposure.

The modified infusion volume, duration, and rate implemented before Part B of the phase 1 study was employed in this phase 2a study, and infusion reactions (IRs) were observed in a minority of subjects (5 subjects [31.3%] receiving TAK-101 and 1 subject [5.6%] receiving placebo). All IRs were mild or moderate (Grade 1 or 2). Infusions were briefly interrupted in 3 subjects receiving TAK-101; all resumed infusion and received the full intended dose. Increases in complement factors C3a and Sc5b9 were seen in most subjects receiving TAK-101 but were not associated with IRs or other AEs.

There were no SAEs observed in the study. The following abnormalities of liver aminotransferases and bilirubin were observed:

TAK-101–treated:

- One subject with Grade 1 elevations of AST, ALT and total bilirubin on end of study visit only, normal on all other visits.
- One subject with Grade 1 elevation of ALT from second infusion through end of gluten challenge, normal at end of study.
- One subject with intermittent Grade 1 elevation of ALT on second infusion visit and end of study visit. Normal on all other visits.
- Two subjects with Grade 1 elevations in ALT at screening visits, normal at end of study.

Placebo-treated:

- Two subjects with Grade 1 elevations of AST and ALT mid study visits (one on Visits 6 and 7, one on Visit 5).
- One subject with Grade 1 elevation in total bilirubin on screening and end of study.

All elevations were asymptomatic and did not result in study discontinuation.

4.2 Rationale for the Proposed Study

Phase 1 and 2a studies have demonstrated an acceptable safety and tolerability profile of TAK-101 and characterized the PK of free gliadin following infusions. The prior phase 2a study demonstrated that TAK-101 given as 8 mg/kg twice with 7 days between doses effectively suppressed gluten-specific T cell activation triggered by gluten challenge compared with placebo. Clinical safety data also showed that TAK-101 was well tolerated, AEs were of mild intensity, and no SAEs were reported. The totality of data support further development of TAK-101. In vitro and nonclinical data have shown hepatotoxicity with a relatively low safety margin compared with the 8 mg/kg dose and suggest TAK-101 at a lower dose could also be efficacious. Given the innovative nature of the TAK-101 nanoparticle platform, to inform dose selection in future studies and understand the benefit-risk profile of TAK-101, the current study has been designed to assess lower dose levels and single-dose regimens that may be active as predicted by nonclinical modeling, and to assess durability of treatment effect, and to confirm the safety and activity seen in the prior phase 2a study.

The key endpoint to explore the dose response relationship will be gluten-specific T cell response to gluten challenge (based on ELISpot) as used in the prior phase 2a study. This analysis may provide evidence supportive of single dose induction, thereby further reducing risk of IR and patient burden. Additional data may include gluten-specific tetramer response, interleukin-2 (IL-2) response and durability of protection from symptoms and IL-2 release with gluten exposure out to 20 weeks post-treatment. These data will provide a robust understanding of the activity and durability of TAK-101 and inform dose selection for future studies.

4.3 Benefit/Risk Profile

Currently there are no approved therapies for CeD, and a significant proportion of patients do not achieve adequate disease control on a GFD. Phase 1 and 2a studies of TAK-101 have demonstrated an acceptable safety and tolerability profile. Phase 2a data demonstrate the ability of TAK-101 to prevent an increase in pathogenic gluten-responsive T cells after gluten exposure which may translate into significant clinical benefit in patients with ongoing active CeD despite gluten avoidance. No SAEs have been observed in the clinical studies to date and the most frequent AEs include mild and transient IRs.

Potential risks of TAK-101 are based on findings of complement activation in the clinical studies and thrombocytopenia and hepatotoxicity in nonclinical studies.

Increased plasma levels of complement (C3a and sC5b9) were observed after the second dose in multiple subjects in both the phase 1 and phase 2a studies. To date, complement activation has not

been associated with AEs or IRs. The risk of greater elevations with subsequent infusions when more than 2 doses of TAK-101 are given is currently unknown. Investigators must be aware of the possibility of IRs and infusions must take place in a monitored setting with appropriate treatment for IRs (including epinephrine) available.

There were no clinically significant abnormalities of liver aminotransferases and bilirubin observed in the phase 1 and 2a studies. This contrasts with significant elevations in liver enzymes seen in nonclinical studies with doses of TAK-101 at 90 mg/kg and above (HED 29 mg/kg) in monkeys and 150 mg/kg and above (HED 24 mg/kg) in rats. The mechanism of liver injury in animals is unknown and is continuing to be investigated. To mitigate risk of liver injury in the current study, subjects with ALT or AST >1 × upper limit of normal (ULN), or total bilirubin >1 × ULN will be excluded and these levels must be tested and remain within the normal range after the first dose of study drug to be eligible to receive the second dose. In addition, the study will be enrolled in a sequential fashion with an initial cohort of 2 mg/kg. This will be followed by a second cohort of 4 mg/kg or placebo if acceptable safety and tolerability is observed in the first cohort, and/or 1 mg/kg or placebo if activity (measured by the Day 20 change from baseline in IFN-γ SFUs) is observed in the first cohort. Throughout the study, and before the initiation of the second cohort, an independent DMC will review unblinded liver test data, and other safety information as appropriate, and make recommendations to the safety management team (SMT) regarding initiation of the second cohort, study continuation, termination of study arm(s) or the entire study, or study modification.

4.3.1 Risk Related to Gluten Exposure

Potential risks of gluten exposure include development of signs and/or symptoms of CeD, including gastrointestinal symptoms and extraintestinal manifestations such as skin rash, neurological/neurocognitive manifestations, elevation in liver aminotransferases and bilirubin, and joint pain. Gluten challenge has been used clinically and in research for decades and in most studies has used longer duration and/or higher dose gluten than in the current study. Any signs/symptoms of study related gluten exposure are expected to resolve promptly after gluten is ceased and is not expected to result in any increase in risk of future complications.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to compare the number of baseline IFN-γ SFUs to the number of IFN-γ SFUs after a 6-day oral gluten challenge among subjects treated with TAK-101 versus placebo.

5.1.2 Secondary Objectives

Secondary objectives of this study are to:

- Evaluate the safety of various dose levels of TAK-101.
- Evaluate gluten-induced CeD symptoms in subjects treated with TAK-101 versus placebo.
- Evaluate change from baseline in gliadin-specific T cell activation following an oral gluten challenge in subjects treated with TAK-101 or placebo.
- Characterize the durability of TAK-101 based on gluten challenge–induced plasma IL-2.
- Characterize the PK of TAK-101.
- Characterize the dose-response relationship of TAK-101 in subjects with CeD on a GFD.
- Assess the immunogenicity of various dose levels of TAK-101.

5.1.3 Exploratory Objectives

Exploratory objectives of this study are to:

- Evaluate change from baseline in celiac serology titers in subjects treated with TAK-101 or placebo.
- Evaluate change from baseline in the percentage of gut-homing CD4, CD8, regulatory and gamma delta (γδ) cells following an oral gluten challenge in subjects treated with TAK-101 or placebo.
- Evaluate changes in CeD symptoms pre- and post-gluten challenge in subjects treated with TAK-101 versus placebo.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is change from baseline (Day 15, or Day 1 in the absence of Day 15) to Day 20 in IFN-γ SFUs based on results of a gliadin-specific ELISpot assay.

5.2.2 Secondary Endpoints

Secondary endpoints include:

- Safety and tolerability as assessed by AEs, IRs, cytokine release syndrome (CRS), physical examinations, vital signs, and clinical laboratory testing, including liver tests.
- Change in Celiac Disease Symptom Diary version 2.1 (CDSD v2.1; 24-Hour Recall) 3-day average score from Day 1 to post-gluten challenge on Day 20, and Weeks 8, 14, and 20 (Postbaseline 3-day average score is counted from the initiation of gluten challenge; Day 1 3-day average score is the average of most recent 3 days before first dose of study treatment).

- Change in CDSD v2.1 (24-Hour Recall) 3-day peak score from baseline to post-gluten challenge on Day 20, and Weeks 8, 14 and 20. (Peak score is the highest score in the 3 days following gluten challenge starting on the initiation of gluten challenge for challenges at Weeks 8, 14, and 20 and the highest score during and the 3 days following the Day 15-20 gluten challenge.) Baseline value will be measured on Day 1.
- Change from pre- to 4 hours post-gluten challenge in plasma IL-2.
- Plasma concentration of TAK-101 after the first and second dose.
- Change in serum concentration of ADAs to TAK-101 (deamidated gliadin peptide [DGP]-IgG) from baseline (before TAK-101 administration).

5.2.3 Exploratory Endpoints

Exploratory endpoints include:

- Change in celiac serology titers from baseline to Week 20.
- Change from baseline in percentage of gut-homing CD4, CD8, regulatory and γδ cells (based on immunophenotyping) following an oral gluten challenge.
- Change from baseline in symptoms evaluated by the Gastrointestinal Symptom Rating Scale (GSRS) and Patient Global Impression of Severity (PGIS) (24-Hour Recall).
- Change in symptoms pre- and post-gluten challenge measured by the CDSD v2.1 (Short Recall), PGIS (Short Recall), and additional exploratory questions.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of TAK-101 for prevention of gluten-specific T cell activation in adult subjects with CeD on a GFD. Two study cohorts are planned for the study, the second of which may include 1 or 2 dose levels, depending on safety, tolerability, and activity observed in the first cohort. A total of approximately 108 subjects with well controlled CeD on a GFD for at least 6 months are planned to be enrolled. Randomized subjects will receive 2 IV infusions of TAK-101 and/or placebo, each separated by 7 days (on Days 1 and 8). Approximately 45 subjects will be randomly assigned initially into 1 of 3 treatment groups with 1:2:2 randomization ratio in the first study cohort:

- Two infusions of placebo.
- One infusion of 2 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 2 mg/kg TAK-101.

A decision will be made to stop the study or continue into the second study cohort by the sponsor SMT (see Section 11.2), taking into account the recommendations of the independent DMC (see Section 11.1). Up to approximately 63 subjects will be randomized into the second cohort.

If it is deemed appropriate to open the second cohort at the TAK-101 4 mg/kg dose level:

The first 22 subjects of the second cohort will be randomly assigned to 1 of 3 treatment groups with 1:2:2 randomization ratio:

- Two infusions of placebo.
- One infusion of 4 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 4 mg/kg TAK-101.

In parallel, the Day 20 change from baseline in IFN-γ SFUs from all subjects in the first cohort will be reviewed by the DMC (unblinded data) and SMT (blinded data), and a decision will be made as to whether a 1 mg/kg treatment arm should be tested.

If the first 22 subjects in the second cohort have been enrolled before this decision is made, then further enrollment will be paused.

If the 1 mg/kg treatment arm is not needed, the remaining 23 subjects will continue to be enrolled into the second cohort and randomly assigned to 1 of 3 treatment groups listed above, with 1:2:2 randomization ratio (there will be a total of 45 subjects in the second cohort). If, however, the 1 mg/kg treatment arm is needed, the remaining 41 subjects will be randomly assigned to 1 of 4 treatment groups with 1:2:2:4 randomization ratio (there will therefore be a total of 63 subjects in the second cohort):

- Two infusions of placebo.
- One infusion of 4 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 4 mg/kg TAK-101.
- Two infusions of 1 mg/kg TAK-101.

If it is decided not to open the second cohort at the 4 mg/kg dose level:

In the event that a decision is made not to proceed to the 4 mg/kg dose level, the Day 20 change from baseline in IFN-γ SFUs from all subjects in the first cohort will be reviewed by the DMC (unblinded data) and the SMT (blinded data), and a decision will be made as to whether to evaluate the 1 mg/kg dose level.

- If 1 mg/kg is recommended to be tested, the second cohort will consist of 45 subjects randomly assigned to 1 of 3 treatment groups with 1:2:2 randomization ratio:
  - Two infusions of placebo.
  - One infusion of 1 mg/kg TAK-101 followed by 1 infusion of placebo.
  - Two infusions of 1 mg/kg TAK-101.

- If 1 mg/kg is not recommended to be tested, the study will terminate enrollment.

Subjects aged 18 to 75 years, inclusive, with documented history of biopsy-proven confirmed CeD, which is well-controlled and on a GFD for a minimum of 6 months will be screened. Eligible subjects who meet all inclusion and no exclusion criteria and provide written informed consent will undergo a single-day 3 g oral gluten challenge approximately 4 weeks before randomization (run-in gluten challenge). Participation in the run-in gluten challenge is a requirement of study participation; however, symptomatic or biomarker response to the run-in gluten challenge will not inform eligibility for randomization. Randomized subjects will receive 2 IV infusions of TAK-101 and/or placebo, each separated by 7 days (on Days 1 and 8). Subjects will be randomly assigned to receive placebo and/or TAK-101 at doses of 2 mg/kg in the first study cohort. In the second study cohort, subjects will be randomly assigned to receive placebo or TAK-101 at a dose of either 4 mg/kg or 1 mg/kg. For both study cohorts, the maximum dose of TAK-101 will be 500 mg per dose. Randomization will be stratified based on HLA type into 3 strata:

1. HLA DQ2/DQ2, DQ2/B1*02, DQ2/DQ8.
2. HLA DQ2/x, B1*02/B1*02, DQ8/B1*02.
3. HLA DQ8/DQ8, DQ8/x.

On Days 15 through 20, subjects will undergo a 6-day gluten challenge by consuming 12 g of gluten daily for 3 days, followed by 6 g of gluten daily for 3 days. Subjects will subsequently undergo single-day 3 g gluten challenges at Weeks 8, 14, and 20. Other than the gluten challenges, subjects will continue to follow a GFD throughout the study.

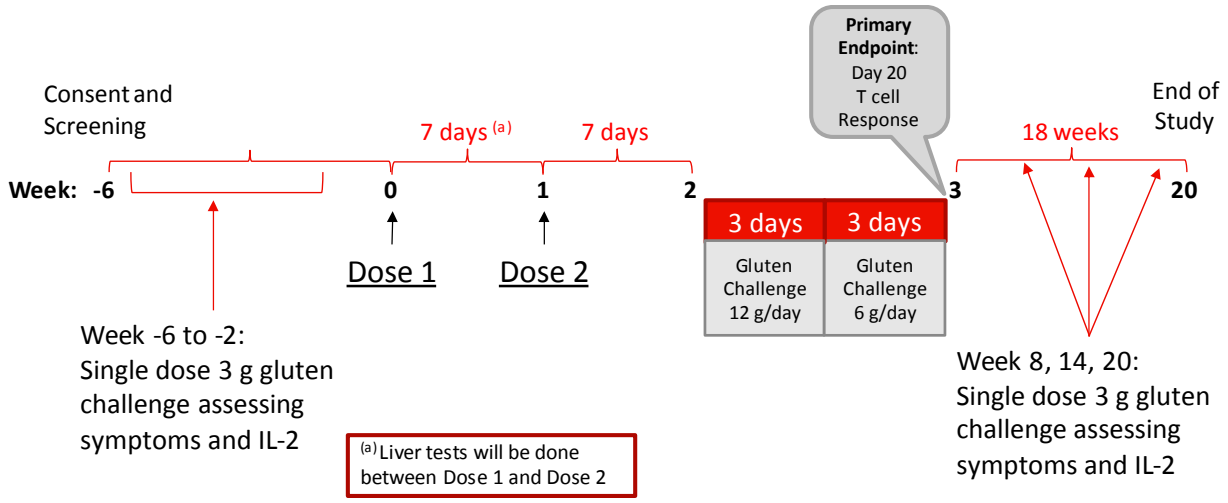
Subjects will be observed for acute AEs, including IRs and CRS, for up to 2 hours following infusion on Days 1 and 8. Subjects will be assessed regularly for safety and tolerability by AEs, physical examination, vital signs, and routine clinical laboratory tests (chemistry, liver tests, and hematology).

Sampling for immunogenicity (ADA assay, DGP-IgG assay), drug-induced CRS, safety laboratory tests for complement levels (C3a, C5a, and SC5b-9), liver tests, analysis of gliadin-specific T cells, blood cell immunophenotyping for gut-homing CD4, CD8, and γδ cells, IL-2 levels, and PK evaluation will be collected as specified in the Schedule of Study Procedures (Appendix A).

Sites will employ all efforts to see subjects as described in the clinical assessments. In unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, exceptions may be granted for alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. These data collected with alternative methods may be handled differently in the final data analysis. This will be documented in the statistical analysis plan.

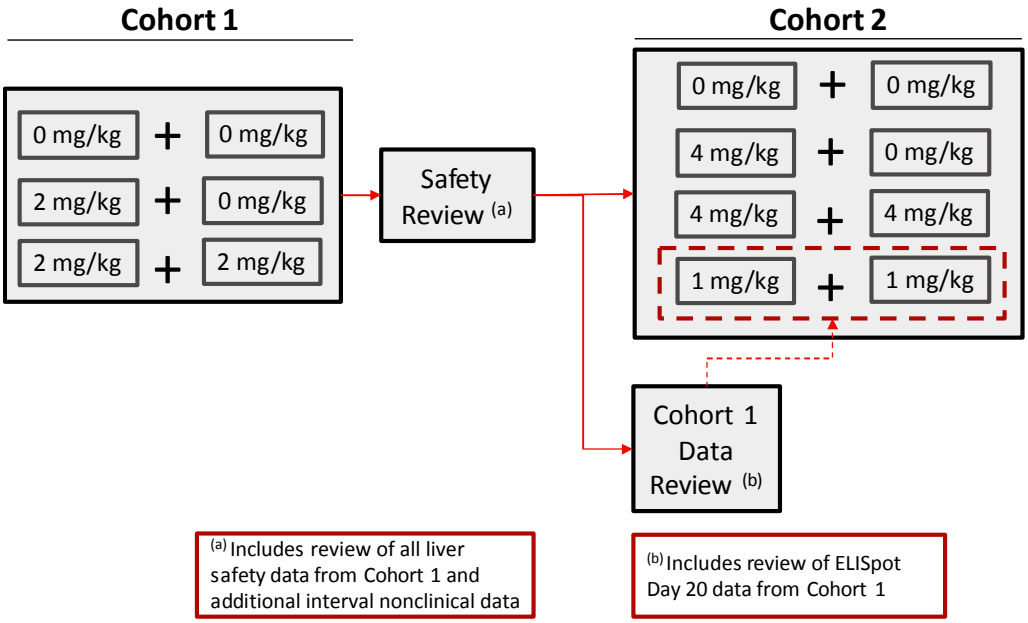
A schematic of the study design is included in Figure 6.a, and a schematic of the study cohorts is presented in Figure 6.b. A schedule of study procedures is listed in Appendix A.

Figure 6.a Schematic of Study Design



IL-2: interleukin-2.

Figure 6.b Schematic of Study Cohorts



ELISpot: enzyme-linked immunospot.

6.2 Justification for Study Design, Dose, and Endpoints

The study population consists of subjects with biopsy-confirmed, asymptomatic CeD and following a GFD. This study population reflects a population most likely to respond to a gluten challenge.

It has been shown in a phase 2a study that TAK-101 given as 8 mg/kg twice with 7 days between doses effectively suppressed T cell activation triggered by gluten challenge compared with placebo. Clinical safety data also showed that TAK-101 was well tolerated, AEs were of mild intensity, and no SAEs were reported. The totality of data support further development of TAK-101. Nonclinical data have shown hepatotoxicity with a low safety margin compared with the 8 mg/kg dose and suggest that TAK-101 at a lower dose could also be efficacious. Therefore, in order to understand the benefit-risk profile of TAK-101 and inform dose selection in pivotal studies, lower dose levels of 2 mg/kg, 1 mg/kg (if included based on recommendation from the DMC) and 4 mg/kg, will be studied sequentially to explore the active dose range of TAK-101 based on T cell response. In addition, the dose cap has been reduced to 500 mg per infusion from the dose cap of 650 mg used in the phase 2a study given the reduction in mg/kg dosing. This dose cap, in addition to the inclusion criterion regarding body mass index (BMI), is to be implemented to avoid administration of substantially higher total doses in overweight individuals compared with other participants.

The decision to include the 4 mg/kg dose will be based on safety data, including liver tests, through Visit 5 from the first cohort and additional nonclinical studies, and the decision to include the 1 mg/kg dose will be based on change from baseline to Day 20 in IFN-γ SFUs from the first cohort.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Study Stopping Rules

Study stopping rules:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- One confirmed case of Hy's law.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study 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 study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for

early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. Biopsy-confirmed CeD that is well-controlled, defined as mild or with no ongoing signs or symptoms felt to be related to active CeD and with IgA tTG <2 × ULN and IgG DGP <3 × ULN.

   Note: Subjects may be retested for IgA tTG and IgG DGP to meet eligibility criteria at the discretion of the investigator.
2. The subject must be on a GFD for ≥6 months.
3. The subject must be HLA-DQ2 and/or HLA-DQ8 positive during screening laboratory testing.
4. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
5. The subject (or, when applicable, the subject's legally acceptable representative) signs and dates a written, informed consent form (ICF) and any required privacy authorization before the initiation of any study procedures.
6. The subject is aged 18 to 75 years, inclusive, at the time of signing the informed consent.
7. The subject weighs at least 40 kg and has a BMI between 16 and 35, inclusive.
8. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent throughout the duration of the study and for 120 days after last dose. The female partner of a male subject should also be advised to use a highly effective/effective method of contraception.*
9. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective/effective method of contraception* from signing of informed consent throughout the duration of the study and for 60 days after the last dose.

   *Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.
10. Other than the condition under study, the subject must be in a good general state of health according to clinical history and physical examination.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Has received any investigational compound within 12 weeks (84 days) before signing of the informed consent.
2. Has received TAK-101 (TIMP-GLIA) in a previous clinical study or as a therapeutic agent.
3. Has presence of inflammatory gastrointestinal disorders or autoimmune diseases, other than well-controlled autoimmune thyroid disease or well-controlled type 1 diabetes mellitus (defined as glycosylated hemoglobin <8 and no hospitalization in the last 12 months for hyper/hypoglycemia).
4. Has known or suspected refractory CeD or ulcerative jejunitis.
5. Has additional food allergies or intolerances that prevent participation in the food challenge.
6. Is receiving ongoing systemic immunosuppressant, systemic (oral or IV) corticosteroid treatment, or has received treatment with systemic immunosuppressants or corticosteroids in the 12 weeks before run-in gluten challenge.
   - Immunosuppressive doses of corticosteroids: more than 3 mg/day budesonide for more than 1 week within 3 months before Dose 1, more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more within 6 months before Dose 1, any dose of oral or IV corticosteroids within 30 days of Day 1, high dose inhaled corticosteroids (>960 µg/day of beclomethasone dipropionate or equivalent), or other immunosuppressive agents.
7. Has known or suspected chronic liver disease or positive for hepatitis B or C. For hepatitis B or C, the subject has 1 of the following at screening:
   - Chronic hepatitis B virus infection defined as being positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody, or
   - Chronic hepatitis C virus (HCV) infection defined as positive for HCV antibody that is confirmed with a positive HCV RNA viral load test (those treated and cured for HCV infection are allowed).
8. Has an ALT or AST >1 × ULN, or total bilirubin >1 × ULN.

   Note: Subjects may be retested to meet eligibility criteria at the discretion of the investigator.
9. Has in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at screening.
10. Has known or suspected immune deficiency syndrome including common variable immune deficiency or HIV infection.
11. If female, the subject has a positive serum pregnancy test at screening or lactating or intending to become pregnant before participating in this study, during the study, and within 60 days after last dose of the study drug; or intending to donate ova during such time period.

12. If male, the subject intends to donate sperm during the course of this study or for 120 days thereafter.
13. Has a history of drug or alcohol abuse that, in the opinion of the investigator, would interfere with the subject's ability to comply with the study requirements.
14. Has received a live vaccine within 28 days prior or a subunit vaccine within 14 days before the first infusion or planned vaccination within 21 days after first infusion.
15. Has known or suspected COVID-19 by the investigator within the past 2 months (additional testing may be performed at the discretion of the investigator). Positive antibody testing for COVID-19 without other evidence of current or recent active infection does not exclude participation.
    a) Subjects who were in screening or run-in period at the time that COVID-19–related factors resulted in discontinuation may also be rescreened with approval of the sponsor or designee.
16. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
17. Has any other significant, uncontrolled organic or systemic medical condition or social circumstance that, in the investigator's opinion, would mean it was not appropriate for the subject to participate in this clinical study.

7.3 Excluded Medications

All prior and concomitant medications, including prescription and nonprescription medicines and vaccines will be reported in the electronic case report form (eCRF) beginning at screening through the final study visit. Subjects must be instructed not to take any digestive enzymes, including over-the-counter (OTC) supplements advertised as for digestion of gluten or protection from gluten exposure.

7.4 Diet, Fluid, Activity Control and Treatment Facilities

All subjects will undergo a single-day 3 g gluten challenge at gluten challenge run-in (Week -6 to -2), a 6-day gluten challenge from Days 15 through 20 (3 days of 12 g/day and then 3 days of 6 g/day), and single-day 3 g gluten challenges at Weeks 8, 14, and 20 to assess persistence of response to therapy. Gluten will be provided in powder form (vital wheat gluten) and consumed in a single meal mixed with water.

With the exception of the gluten challenge as described above, all subjects must adhere to a GFD throughout the study (see Table 7.a). There are no other restrictions on food or fluid intake during the study.

Gluten-Free Diet

Gluten is a protein found in wheat, barley, rye and the derivatives of these grains, including malt and brewer's yeast.

Table 7.a Gluten-free Grain Alternatives

Almond meal flour	Millet
Amaranth	Pea flour
Brown, white, and wild rice	Potato flour
Buckwheat	Potatoes
Coconut flour	Quinoa
Corn	Sorghum
Cornstarch	Soy flour
Guar gum	Teff

Other dietary elements of a GFD include fruits, vegetables, meats, poultry, fish, beans, legumes and most dairy products.

Products labeled as "gluten-free," must not exceed 20 mg/kg of gluten or 20 ppm (milligrams of gluten per kilogram of product).

7.5 Criteria for Discontinuation of Study Drug

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.17.

1. AE.

- Subjects who experience an AE may require early discontinuation because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the AE.
- IRs:
  - Subjects with anaphylaxis or National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or higher IRs on the first infusion will not receive a second infusion.
- Subjects with liver test abnormalities should be evaluated to determine whether study drug should be continued, interrupted, or discontinued. See Appendix E.
- Subject will have liver enzymes/bilirubin tested on Day 3 (2 days [±1] after first infusion) and again before the second dose.
  - To be eligible for the second study drug infusion on Day 8, post-first infusion liver enzymes/bilirubin must be confirmed to be ≤1.2 × ULN.

- If liver tests are 1.2 to 2 × ULN on Day 3, at the investigator's discretion repeat testing may be performed 1 to 2 weeks later following the algorithm in the Appendix E. The second infusion can be given if these are within inclusion criteria.
- Subjects whose liver enzymes/bilirubin do not meet these criteria will not receive further infusions.

2. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. 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 documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
   - 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 due to an AE should not be recorded in the "voluntary withdrawal" category; similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.
   - Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.
7. Other.
   - Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Criteria for Withdrawal of a Subject from the Study

Subjects should be followed for efficacy and safety for all scheduled visits after study drug administration, even if subjects have discontinued study drug early. The primary reason for withdrawal of the subject from the study should be recorded in the eCRF using the following categories.

1. 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 documents.
2. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
3. Study termination. The sponsor, IRB, or regulatory agency terminates the study.

4. Death.
5. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.7 Procedure for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study 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 study. 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. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

TAK-101 active drug product will be provided to the site by the sponsor. TAK-101 placebo is 0.9% sodium chloride injection. Details regarding the dosage form, strengths, composition for the extemporaneous preparation, packaging and labeling of the active drug and placebo can be found in the pharmacy manual or in the referenced compounding manual when applicable. Study drug will be packaged to support enrollment and replacement of subjects as required.

8.1.1.1 TAK-101

The sponsor will supply TAK-101 to the study site in an open-label manner. TAK-101 is a lyophilized powder in a glass vial containing approximately 100 mg of TAK-101 particle (approximately 1 mg gliadin) with cryoprotectant excipients. TAK-101 will be in a labeled glass vial and packaged in an appropriately labeled carton including but not limited to the sponsor's name, address, protocol number, lot number, product name, strength of the product, and caution statement and storage conditions.

8.1.1.2 Placebo

The placebo for this study is 0.9% sodium chloride injection USP (normal saline). The 0.9% sodium chloride injection will be sourced by the study site to prepare for placebo.

8.1.1.3 Management of IRs

Subjects must be monitored closely for signs and symptoms of an IR. In the event of an IR, the infusion should be slowed, or stopped and restarted at a slower rate (25% of prior rate) at the discretion of the investigator. Infusion can be restarted at any point after signs and symptoms of an IR resolve, up to 2 hours after interruption. If a severe IR occurs (NCI CTCAE Grade 3 or 4 signs or symptoms), discontinue infusion and institute treatment as needed. NCI CTCAE Grade 3 and 4 IRs will be considered adverse events of special interest (AESIs; see Section 10.1.5). NCI CTCAE grading is shown in Appendix L. If a subject experiences an IR of Grade 2 or higher in intensity, the sponsor should be notified immediately.

In addition, if a subject experiences an IR, the following procedures will be undertaken:

- A symptom-driven physical examination to capture medically relevant details, including but not limited to, a thorough dermatologic examination; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.
- Vital signs (sitting or supine blood pressure, heart rate, and body temperature) will be captured at the time of the IR and at least every 15 minutes until the resolution or stabilization of the IR.
- Blood samples for CRS, and for C3a, C5a, and SC5b-9 complement levels will be drawn at the time of the IR.

The investigator may administer any medically indicated pharmacologic agent or procedure intended to relieve symptoms (CAUTION: no other drugs may be mixed in the investigational medicinal product (IP) infusion bag). Signs and symptoms of the IR and drugs given for treatment are to be recorded in the medical record and in the eCRF.

Subjects experiencing an NCI CTCAE Grade 3 or 4 IR should be discontinued from further doses of IP. After the first experience of an IR that is ≤ Grade 2, the investigator may elect to initiate the next infusion at a slower rate (start at 25% of rate in Section 8.1.1.1). All changes to infusion rate are to be recorded in the medical record and in the eCRF.

> Note: If an infusion is stopped and then resumed, the time of stopping and resuming should be recorded in the CRF.

8.1.1.4 Rescue Medications

In some cases, study participants may have severe reactions to study administered gluten necessitating treatment. Common symptom seen during gluten challenge studies include nausea, vomiting, abdominal pain, diarrhea, headache and fatigue. These symptoms may be treated using approved treatments and subjects may remain in the study as long as no excluded medications are administered eg, any corticosteroids, including budesonide. Medications which may be considered include 5-HT3 antagonists such as ondansetron, gastrointestinal antispasmodics such as dicyclomine and antidiarrheal agents such as loperamide. Use of medications should be restricted to treatment of significant symptoms which may otherwise result in study discontinuation and should not be used prophylactically before gluten exposure. All medications used for treatment of gluten related symptoms should be documented in the eCRF.

8.1.1.5 Challenge Agents

Gluten will be provided in powder form (vital wheat gluten) and consumed in a single meal mixed with water (details on preparation of gluten will be contained in the pharmacy manual).

All subjects will undergo a single-day 3 g gluten challenge during run-in (Weeks -6 to -2) and at Weeks 8, 14, and 20 to assess persistence of response to therapy through assessment of T cell activation. Single-day 3 g gluten challenges will be administered at the site of blood testing, either in clinic or at home. Beginning at Week 2, subjects will also undergo a 6-day gluten challenge with 12 g/day for 3 days followed by 6 g/day for 3 days. The first dose of the 6-day gluten challenge will be administered in the clinic and the following 5 days of gluten challenge will be administered at home. There will be a minimum washout period of 2 weeks between gluten challenges.

8.1.1.6 Sponsor-Supplied Drugs

Sponsor supplied drug is TAK-101 and is summarized in Section 8.1.1.1.

8.1.2 Storage

TAK-101 must be stored at 2°C to 8□ (36°F-46°F) and protected from light in a secure, temperature-monitored, limited access location. A daily temperature log must be maintained, and temperature excursions documented.

Placebo (0.9% sodium chloride) should be stored at ambient room temperature in accordance with the product label.

8.1.3 Dose and Regimen

TAK-101 or placebo will be administered at the following escalating rates:

- 20 mL per hour for 15 minutes, then
- 40 mL per hour for the next 15 minutes, then
- 80 mL per hour for the duration of the infusion (approximately 2 hours).

The total infusion time will be approximately 2.5 hours. The site should check the infusion pumps at regular intervals to ensure that the infusion is being administered to the subject, as planned. Additional instructions will be provided in the pharmacy manual provided by the sponsor.

Subjects in the first study cohort will be randomized into 1 of 3 treatment groups:

- Two infusions of placebo.
- One infusion of 2 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 2 mg/kg TAK-101.

After the decision is made to continue into the second study cohort at the 4 mg/kg dose level, up to approximately 63 subjects may be randomized into the second cohort. The first 22 subjects of the second cohort will be randomly assigned to 1 of 3 treatment groups in the second cohort:

- Two infusions of placebo.
- One infusion of 4 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 4 mg/kg TAK-101.

If a decision is made that the 1 mg/kg treatment arm should not be tested, the remaining 23 subjects will continue to be enrolled into the second cohort and randomly assigned to 1 of 3 treatment groups listed above, with 1:2:2 randomization ratio (total of 45 subjects in second cohort). If, however, the decision is made to enroll subjects at the 1 mg/kg dose level in the second cohort, the remaining 41 subjects will be randomly assigned to 1 of 4 treatment groups in the second cohort:

- Two infusions of placebo.
- One infusion of 4 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 4 mg/kg TAK-101.
- Two infusions of 1 mg/kg TAK-101.

If a decision is made not to proceed to the 4 mg/kg treatment arms, and that the 1 mg/kg treatment arms should be tested instead, the second cohort would consist of 45 subjects being randomly assigned to 1 of 3 treatment groups:

- Two infusions of placebo.
- One infusion of 1 mg/kg TAK-101 followed by 1 infusion of placebo.
- Two infusions of 1 mg/kg TAK-101.

The dose and regimen are summarized in Table 8.a.

Table 8.a Dose and Regimen

Cohort 1 Treatment Groups	Dose	Treatment Description
A	Placebo	0.9 % sodium chloride injection infusion on Days 1 and 8
B	2 mg/kg TAK-101, Placebo	TAK-101 2 mg/kg infusion on Day 1 followed by 0.9% sodium chloride injection infusion on Day 8
C	2 mg/kg TAK-101	TAK-101 2 mg/kg infusion on Days 1 and 8
Cohort 2 Treatment Groups	**Dose**	**Treatment Description**
A	Placebo	0.9 % sodium chloride injection infusion on Days 1 and 8
D	4 mg/kg TAK-101, Placebo	TAK-101 4 mg/kg infusion on Day 1 followed by 0.9% sodium chloride injection infusion on Day 8
E	4 mg/kg TAK-101	TAK-101 4 mg/kg infusion on Days 1 and 8
F	1 mg/kg TAK-101	TAK-101 1 mg/kg infusion on Days 1 and 8
G	1 mg/kg TAK-101	TAK-101 1 mg/kg infusion on Day 1 followed by 0.9% sodium chloride injection infusion on Day 8

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented in the Dosing section of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically. The overdosed subject should be followed up for liver safety monitoring (ALT, AST, direct and total bilirubin, and ALP) on Day 2 or 3 after the dosing date and then retested after 3 to 5 additional days. Suspected cases of liver injury should be closely followed and treated.

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or designee will use the interactive response technology (IRT) to randomize the subject into the study at Visit 3 (Day 1/Week 0). The medication identification number of the study drug to be dispensed will then be provided by the IRT. If sponsor-supplied drug is lost or damaged, the site can request a replacement via the IRT (refer to the IRT manual provided separately). At Visit 4 (Day 8, Week 1), the investigator or designee will again access the IRT to request

additional study drug for each subject. The medication identification number of the study drug to be dispensed will be provided by the IRT.

8.3 Randomization Code Creation and Storage

Randomization personnel of the designee of the sponsor will generate the randomization schedule; the IRT will be used in a centralized fashion for subject randomization and study medication assignments. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

Randomization and treatment assignment will be managed by the IRT.

Investigators, subjects, and all study staff with direct subject contact will be blinded to treatment assignment. In accordance with the pharmacy manual provided by the sponsor, a designated unblinded pharmacist (or otherwise qualified personnel) at each site will prepare each dose. That individual should have no contact with the subjects and minimize contact with other site study personnel.

Because TAK-101 is an opaque milky white suspension once reconstituted and diluted, and the placebo is a clear solution (normal saline), both the IV bag containing IP and the IV tubing will be covered at the time the IP leaves the pharmacy and remain covered throughout treatment administration.

Since the maintenance of the blind may be compromised because of results from drug concentrations and biomarker assessments, such results should not be disclosed to the investigator before blind breaking. In the event that results must be reported to the investigator before breaking the blind, all efforts should be made to maintain the blind (eg, as changing a medication ID number in order to avoid identification of subjects by the laboratory site personnel). Detailed procedures for measuring subject drug concentration levels, (including reporting results) are provided in the separately created procedure for directions on handling of biological samples for measuring drug concentrations and biomarker assessments.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by the investigator, by accessing the IRT.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the eCRF/IRT.

If any site personnel are unblinded, study drug must be stopped immediately, and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, TAK-101 for IV infusion, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment (by signing bottom half of the packing list and faxing per instructions provided on the form or by recording in the IRT). If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication ID/job number used to prepare each dose.
- Verifying that all containers used/assigned are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date, date and amount dispensed including initials, seal, or signature of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs

are destroyed at the site or returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained before the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth and age at time of informed consent, sex, Hispanic/Latino ethnicity, race as described by the subject, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or before informed consent or are ongoing at the time of informed consent. The date, method and reason for CeD diagnosis will be recorded, and the duration the subject has been on a GFD will also be recorded. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 90 days before signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment before first dose examination.

9.1.4 Vital Sign Procedure

Vital signs will include body temperature (oral or tympanic measurement), respiratory rate (supine/semisupine), blood pressure (systolic and diastolic) and pulse (beats per minute). Vital signs can be performed in supine or semisupine position but should be performed after resting for 5 minutes and consistently for each subject.

When vital signs are scheduled at the same time as blood sampling, the blood sampling will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below: Height is recorded in centimeters without decimal places. Weight is collected in kilograms with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

The eCRF will perform the BMI calculation based on the height and weight values entered.

9.1.5 Primary Efficacy Measurement

The primary efficacy measurement will be the change from baseline to Day 20 in IFN-γ SFUs based on results of a gliadin-specific ELISpot assay. The primary endpoint will be compared between each TAK-101 arm and the placebo arm using the Wilcoxon rank-sum test using the biomarker analysis set. The Hodges-Lehmann estimator of location shift and the associated 95% CI will be used to estimate the treatment difference between each TAK-101 dose arm and placebo.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vaccinations, vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at the screening/baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be documented. Serologic or direct viral testing for COVID-19 may be performed at screening according to site guidance and/or the discretion of the investigator.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual. Subjects are not required to fast for laboratory safety tests, but fasting status should be documented.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	ALT	Albumin
White blood cells including differential	Albumin	Protein
	ALP	Glucose
Hemoglobin	AST	pH
Hematocrit	Total and direct bilirubin	Leukocytes
Platelets	Glucose	Blood
Coagulation (D-dimer, PT, PTT, fibrinogen)	Total protein	Bilirubin
	Creatinine	Urobilinogen
	Blood urea nitrogen	Ketone
	Creatine kinase	Creatinine
	GGT	
	Potassium	
	Sodium	

Other:

Whole Blood:
Testing for HLA-DQ2/HLA-DQ8

Plasma:
Histamine

Serum	Urine
HIV test (confirmatory testing is allowed; most sensitive test should take precedence).	Female subjects only: hCG (for pregnancy)
Hepatitis panel, including HBsAg, anti-HBcAb and anti-HCV if required	Drug screen including: amphetamines (including methamphetamine), barbiturates, benzodiazepines, cocaine, marijuana, 3,4-methylenedioxymethamphetamine, morphine, oxycodone, buprenorphine, phencyclidine, propoxyphene, tricyclic antidepressants [a]
Female subjects only:	
Beta hCG (for pregnancy) for female subjects of childbearing potential	
FSH (if menopause is suspected)	
Celiac serologies (IgA tTG, IgA DGP, IgG DGP)	
C-reactive protein	
Tryptase	

ALT: alanine aminotransferase; ALP: alkaline phosphatase; anti-HBcAb: antibody to hepatitis B core antibody; AST: aspartate aminotransferase; DGP: deamidated gliadin peptide; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; IgA: immunoglobulin A; IgG: immunoglobulin G; PT: prothrombin time; PTT: partial thromboplastin time; tTG: tissue transglutaminase.

[a] See Section 7.2 for exclusion criteria regarding eligibility based on results of the drug screen.

Laboratory samples will be analyzed at a central laboratory (tests may be performed at local laboratories for safety evaluation if it is not possible to have them performed at the central laboratory) and the results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. With exception of postdose celiac serologies results which are unblinding, these will be filed at the end of the study (after final database lock).

For subjects with treatment-emergent ALT elevations ≥3 × ULN, see Appendix E for additional monitoring, evaluation, and follow-up recommendations.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 120 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.9.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 60 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below).

In addition, they must be advised not to donate ova during this period.

9.1.9.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless 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 aged <45 years) 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.

** Sterilized males should be at least 1-year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
    - Non-Hormonal Methods.
        - Intrauterine device.
        - Bilateral tubal occlusion.
        - Vasectomized partner (provided that partner is the sole sexual partner of the study participant) and that the vasectomized partner has received medical assessment of the surgical success.
    - Hormonal Methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months.
            - Oral.
            - Intravaginal (eg, ring).
            - Transdermal.
        - Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
            - Oral.
            - Injectable.
            - Implantable.
2. Unacceptable methods of contraception are:
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge without spermicide and without condom.

- Sexual abstinence is NOT an acceptable method of contraception.

3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova and sperm donation during the course of the study.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   - Contraceptive requirements of the study.
   - Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   - Assessment of subject compliance through questions such as
     – Have you used the contraception consistently and correctly since the last visit?
     – Have you forgotten to use contraception since the last visit?
     – Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
     – Is there a chance you could be pregnant?
5. In addition to a negative serum hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses) and a negative urine hCG pregnancy test before receiving any dose of study medication (as close as possible and before first dose of study medication, preferably on the same day).

9.1.10 Pregnancy

If any subject is confirmed to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 120 days after the last dose, should also be recorded following authorization from the subject’s partner.

If the pregnancy occurs during administration of active study drug, eg, after the randomization visit, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded at baseline before the first infusion and then only if any related AEs occur, including IRs. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Abnormal and clinically significant findings should be documented as an AE.

9.1.12 Biomarker Collection

Blood samples and urine to evaluate biomarkers will be collected as described in the laboratory manual at times noted in the Schedule of Study Procedures (Appendix A). The primary specimen collection is presented in Table 9.b.

Table 9.b Primary Specimen Collection Table

Specimen #	Specimen name in Schedule of Procedures	Primary specimen	Primary specimen derivative	Description of intended use	Sample collection
1	Blood sample for immunophenotyping, tetramer staining and ELISpot	Blood	PBMC	Biomarker measurements	Mandatory
2	Blood sample for HLA typing	Blood	DNA	HLA-typing	Mandatory
3	Blood sample for RNA	Blood	RNA	Biomarker measurements	Mandatory
4	Plasma sample for protein	Plasma	NA	Biomarker measurements	Mandatory
5	Urine sample for gluten	Urine	NA	Gluten exposure	Mandatory
6	Plasma sample for gliadin PK	Plasma	NA	PK measurements	Mandatory
7	Serum sample for immunogenicity	Serum	NA	PK measurements	Mandatory

ELISpot: enzyme-linked immunospot; NA: not applicable; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetic(s).

9.1.12.1 Blood Sample for Immunophenotyping, Tetramer Staining, and ELISpot

PBMCs will be collected before and at 6 days after first day of the 6-day gluten challenge, a time point when gluten-specific T cells and gut-homing T cells in the blood are near maximum levels. These samples may be used for multiple analyses including the following:

For quantifying gluten-specific T cells, ELISpot analysis will measure T cells that respond to ex vivo treatment with gluten peptides and produce IFN-γ. These T cells are likely responsible with the pathology associated with CeD. If done, ELISpot analysis for T cells that produce interleukin-10 after ex vivo gluten peptide treatment will also be evaluated. These T cells may contribute to tolerance induction. HLA-DQ2 tetramers complexed with gluten peptides may be used to quantify blood T cells which are gluten-specific and characterize expression of markers for regulatory T cells and of activation, exhaustion and gut homing.

Immunophenotyping PBMCs may be done to characterize T cell sub-populations that change with gluten challenge including those with activated, gut homing γδ, CD4, CD8 and regulatory phenotypes as well as cells of other lineages.

9.1.12.2 Blood Sample for HLA Typing

As part of screening procedure, a blood sample will be collected from each subject and the DNA evaluated for HLA-DQ2.5 and/or HLA-DQ8. Most patients with CeD are positive for HLA-DQ2 (>90%) with the rest having HLA-DQ8 (5%-10%) or half of the DQ molecules. The presence of these MHC Class II proteins is required for a diagnosis of CeD, but presence alone is not sufficient for diagnosis. These data will be included as part of the CSR.

9.1.12.3 Blood Cell Collection for RNA

The blood samples for RNA will be collected in a separate sample but at the same time as the plasma samples for protein. These samples may be used to explore other changes in the blood that correspond with the acute changes as exemplified by IL-2. These samples may also be used for additional analysis to understand pharmacology and/or disease biology. The conclusions from these studies, if performed, will be ad hoc and not included in the CSR.

9.1.12.4 Plasma Sample for Protein

IL-2 levels in the plasma will be tested before and 4 hours after gluten challenge. Levels of other cytokines may also be tested. IL-2 is acutely induced in patients with CeD and detected in the blood within 4 hours. Other cytokines are increased in some patients but are less consistent and less characterized.

9.1.12.5 Urine Sample for Gluten

Urine samples will be collected from subjects and tested for gluten peptides as evidence of unintentional or, during gluten challenge, intentional gluten exposure.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Plasma for PK Sampling

Blood samples to evaluate the PK of gliadin in plasma will be collected at Weeks 0 and 1. Plasma PK samples will be collected predose, 30 minutes after start of the infusion, and at end of infusion on each drug treatment visit. Predose samples should be collected within 30 minutes before dosing. Generally, PK samples should not be collected from the arm where the TAK-101 infusion is administered. The actual dates and times of dosing (start and end of infusion) and sampling times must be accurately recorded in the eCRF. If the infusion is interrupted, the time of stopping and resuming should be also recorded (any interrupted infusion must be resumed during the same study visit).

9.1.14 Immunogenicity Sample Collection

9.1.14.1 Serum Sample for Immunogenicity

Blood samples will be collected and tested for antibodies directed against gliadin to detect ADA and these results will be included as part of the CSR. These samples may also be used to develop new or refine the present immunogenicity assay.

9.1.15 Patient-Reported Outcomes Instruments

9.1.15.1 CDSD v2.1 (24-Hour and Short Recall)

The CDSD v2.1 is an 8-item, self-administered questionnaire that evaluates the following CeD symptoms: bowel movement frequency, vomiting, diarrhea, abdominal pain, bloating, nausea, and tiredness. Symptom severity is evaluated using 5-point Likert-type scales (none, mild, moderate, severe, and very severe) for all items except for frequency questions relating to stool counts, diarrhea, and vomiting frequency. The CDSD v2.1 (24-Hour Recall) (Appendix F) evaluates these symptoms over the previous 24 hours. It will be administered as part of the daily diary for the duration of the study, including screening/run-in, treatment, and follow-up periods. The CDSD v2.1 (Short Recall) (Appendix G) evaluates these symptoms over the previous 2 hours. For each single-day 3 g gluten challenge, the CDSD v2.1 (Short Recall) will be administered before and 2 and 4 hours after the challenge. The CDSD v2.1 (Short Recall) will also be administered before and 2 and 4 hours after the first dose of the 6-day gluten challenge.

9.1.15.2 PGIS (24-Hour and Short Recall)

The CeD PGIS is a 1-question instrument that evaluates the overall patient perception of symptom severity. Response options are measured using a Likert-type scale (no symptoms, mild, moderate, severe, very severe). The PGIS (24-Hour Recall) evaluates symptom severity over the previous 24 hours and will be administered at the visits indicated in the Schedule of Study Procedures (Appendix A). During run-in, the PGIS (24-Hour Recall) will be administered on the day immediately before and within 24 hours after gluten challenge. The PGIS will be administered before any other scheduled procedure. Additionally, for each single-day 3 g gluten challenge, the

PGIS (Short Recall) (Appendix I) will be administered before and 2 and 4 hours after the challenge. The PGIS (Short Recall) will also be administered before and 2 and 4 hours after the first dose of the 6-day gluten challenge.

9.1.15.3 CeD GSRS

The GSRS is a non–disease-specific 15-item instrument measuring the discomfort of gastrointestinal symptoms using a Likert scale (no discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, severe discomfort, very severe discomfort). In this study, the 10 items relevant to CeD will be evaluated (stomach pain/discomfort, hunger pains, nausea, rumbling in stomach, bloating, burping, passing gas, diarrhea, loose stools, urgent bowel movement) (Appendix H). The CeD GSRS will be administered in clinic at screening (Visit 1), on Day 1 (Visit 3 baseline visit), on Day 15 (before the gluten challenge), on Day 20 within 24 hours or on the day immediately after completion of the gluten challenge, and at Visit 9 (end of study).

9.1.15.4 Additional Exploratory Questions

Additionally, for each single-day gluten challenge, the additional exploratory questions will be administered before the challenge and then 2 hours and 4 hours following the challenge. The questions evaluate the symptoms of irritability and cognitive function (using the same scale as the CDSD v2.1, 6-point Likert-type scale; Appendix K).

9.1.16 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the eCRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pretreatment event (PTE)/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.1.17 Documentation of Study Entrance/Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

Please refer to the study manual provided.

9.2 Gluten Exposure Compliance

On Day 15 of the 6-day gluten challenge subjects will consume gluten in the clinic, on Days 16 through 19 subjects will consume gluten at home, and on Day 20 of the 6-day gluten challenge subjects will consume gluten either at home before coming to the clinic or in the clinic. Subjects will be required to document consumption of gluten in the subject home daily diary. In addition, urine samples for assessment of gluten exposure will be collected in the clinic on Day 15 of the 6-day gluten challenge (pre-dose), Day 17 at home, and Day 20 at home or in clinic.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

An accurate gluten disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. At the completion of the study, all unused gluten will be returned to the sponsor (or designee) or disposed of by the site in accordance with the sponsor's (or designee's) written instructions.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

In acknowledgement of hospital, local, state, or national government restrictions or other site-related factors caused by unavoidable circumstances (ie, COVID-19 pandemic) which may prevent investigators from conducting the study according to the Schedule of Study Procedures at the clinical study site, investigators may seek approval from the medical monitor and/or sponsor to continue subjects in the study despite departure from the Schedule of Study Procedures. Investigators are expected to evaluate the impact to the safety of the study subjects and site personnel for subjects to continue. In evaluating such requests, the medical monitor will give the highest priority to the safety and welfare of the subjects. For subjects that are impacted, any procedures not conducted per the original study plan will be documented in the study records.

When approval is given for a subject to miss an in-person study visit, a healthcare provider will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact, the study site physician or other qualified site staff should also at minimum conduct the following assessments: AE collection and concomitant medication documentation. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Additionally, sites may have study personnel see the subject outside of the on-site clinic to conduct study assessments contingent upon local regulations. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such

departures will be recorded in the study records. Alternatively, sites may seek approval to extend the visit window in order to conduct an on-site visit.

9.3.1 Post-Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or 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 a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or 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 or ECG re-test and/or continued monitoring of an abnormal value or finding 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 a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").

- If the subject experiences a worsening or complication of an AE after any change in study drug, 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 intensity of AEs/Serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

AEs related to gluten exposure

- AEs related to gluten may be anticipated to include signs and/or symptoms of CeD, including gastrointestinal symptoms and extraintestinal manifestations such as skin rash, headache, fatigue neurological/neurocognitive manifestations, elevation in liver function tests (LFTs), and joint pain. Symptoms collected through the CDSD v2.1, including diarrhea, bowel movement frequency, abdominal pain, bloating, nausea, and fatigue that occur with gluten exposure should not be reported as AEs unless these events become serious.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or 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 PTEs or AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

Anticipated AEs

- 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 LFTs, 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.

10.1.4 SAEs

An 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. Leads to 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.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
COVID-19 pneumonia	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19–related disease	Spontaneous abortion/stillbirth and fetal death

AE: adverse event; COVID-19: coronavirus disease 2019.
Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 AESIs

An AESI (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

For this study, AESIs include signs and symptoms of liver injury and IRs.

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized according to NCI CTCAE v5.0 (Appendix L) and in addition liver AEs will be characterized per Food and Drug Administration (FDA) guidelines (Appendix L).

10.1.7 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as gluten exposure, underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures including gluten exposure should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.

- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE 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 study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Visit 3, Day 1) or until screen failure. For subjects who discontinue before study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Visit 3, Day 1). Routine collection of AEs will continue until Visit 9, Week 20.

10.2.1.2 PTE and AE Reporting

At each study 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 study. Subjects experiencing a serious PTE 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.

Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug 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 PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

CDSD Version 2.1, CeD GSRS, and PGIS Version 1.1 will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 AESIs

If the AESI (see Section 10.1.5), which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in an AESI Form or an SAE Form. The Form should be completed and reported to the clinical contract research organization (CRO)/pharmacovigilance department within 24 hours.

Special interest AE/abnormality criteria include:

- Laboratory value threshold, if applicable.
- Premature termination for the AESI, if applicable.
- Any other specific criteria.

AESIs must be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

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

A Takeda 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 study drug(s)
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

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

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal LFTs

For any subject with ALT ≥3 × ULN ***AND*** total bilirubin ≥2 × ULN ***OR*** international normalized ratio (INR) >1.5 × ULN for which an alternative etiology has not been found, report the event as an SAE, contact the medical monitor and Takeda study clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix E.

10.3 Follow-up of SAEs

If information 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.

10.3.1 Safety Reporting to Investigators, IRBs, 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, as applicable, in accordance with national regulations in the countries where the study 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 to the regulatory authorities as expedited report 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 a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IRB in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 DMC

An external DMC will be used during this study to allow study team members to remain blinded to subject treatment during the study. The DMC will review unblinded interim safety data and Day 20 activity data (ELISpot SFUs) from the first cohort. The DMC will perform these duties in addition to the customary duties of safeguarding the interest of study participants, assessing the safety of the interventions during the study, and for monitoring the overall conduct of the clinical study. The DMC will provide recommendations about stopping or continuing the study or treatment groups, including initiation of the second study cohort. To make the recommendation to start the 4 mg/kg arm of the second cohort, the DMC will be reviewing the first approximately 30 subjects who have completed Visit 5 liver tests or have early terminated by Visit 5. To make the recommendation to start the 1 mg/kg arm, the DMC will be reviewing activity data from the first cohort. To enhance the integrity of the study, the DMC may also formulate recommendations relating to the study conduct.

Details of the DMC including meeting frequency will be captured in a charter before the start of the study.

11.2 SMT

The decision to proceed with either dose arm of the second cohort will be made by the SMT. The SMT will review DMC recommendations, emergent nonclinical data including reversibility, and all liver safety data from each cohort in a blinded manner before dosing the subsequent cohort.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

The sponsor or its designee will supply study sites with 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 study 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 Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs 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 e-sign 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 study 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 (Data Clarification Form provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study 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.

12.2 Record Retention

The following procedure is applied for the countries except for Japan.

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-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 drug 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, International Conference on Harmonisation (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 study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before unblinding of subjects' treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before unblinding of subjects' treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The full analysis set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postbaseline measurements. Subjects will be analyzed according to the treatment they were randomized to receive.

The safety analysis set will consist of all subjects who received at least 1 dose of study drug. Subjects will be analyzed according to actual treatment received.

The biomarker analysis set will consist of all subjects who have baseline and Day 20 ELISpot assay results. Subjects will be analyzed according to the treatment they were randomized to receive.

The PK analysis set is defined as all randomized subjects who received at least 1 dose of study drug and for whom there is at least 1 reported PK concentration. Subjects will be analyzed according to actual treatment received.

The per protocol set (PPS) will include all subjects in the biomarker analysis set who had no major protocol violations in a way that would impact the study output significantly. All decisions to exclude subjects for the PPS will be made before the unblinding of the study.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for FAS and the biomarker analysis set.

The following demographic characteristics will be summarized in the following order in the tables: age (years), age (categorical), sex, ethnicity, race, weight (kg), height (cm), and BMI (kg/m^2). In addition, other baseline characteristics will be summarized.

13.1.3 Efficacy Analysis

The primary efficacy analysis will be based on the biomarker analysis set, and all other efficacy analyses will be based on the FAS unless stated otherwise. Unless otherwise specified, baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment before taking the first dose of TAK-101.

All efficacy analyses will be conducted according to the treatment assigned.

All statistical tests will be 2-sided hypothesis tests conducted at the 5% level of significance for main effects. All CIs will be 2-sided 95% CIs, unless stated otherwise.

Primary Efficacy Analysis:

The primary endpoint is change from baseline (Day 15, or Day 1 in the absence of Day 15) to Day 20 in IFN-γ SFUs. The primary endpoint will be compared between each TAK-101 arm and the placebo arm using the Wilcoxon rank-sum test using the biomarker analysis set. The Hodges-Lehmann estimator of location shift and the associated 95% CI will be used to estimate the treatment median difference between each TAK-101 dose arm and placebo. Descriptive statistics will also be used to summarize the primary efficacy endpoint. Missing data will not be imputed.

Multiplicity will be adjusted using the fixed-sequence testing procedure to compare each treatment arm with the placebo arm. All tests will be performed at the 0.05 level in the sequence below. If any hypothesis test in this sequence is not significant, all subsequent tests will not be performed; however, p-values will still be presented and are regarded as descriptive.

1. TAK-101 4 mg/kg 2 infusions versus placebo.
2. TAK-101 4 mg/kg 1 infusion versus placebo.
3. TAK-101 2 mg/kg 2 infusion versus placebo.
4. TAK-101 2 mg/kg 1 infusion versus placebo.
5. TAK-101 1 mg/kg 2 infusions versus placebo.
6. TAK-101 1 mg/kg 1 infusion versus placebo.

If any treatment group is not opened or terminated early, hypothesis testing of the treatment group will not be performed and analysis will proceed with the next dose tested in the fixed-sequence testing specified above.

Sensitivity analyses will include repeating the primary efficacy analysis based on the PPS, and using an analysis of covariance (ANCOVA) approach based on the FAS. The ANCOVA model will include TAK-101 treatment dose, schedule, and stratification factor as fixed effects, and baseline measurement as covariate. Missing endpoint values will be imputed by multiple imputation.

Secondary Efficacy Analyses:

The secondary efficacy endpoints will be compared between each TAK-101 arm and the placebo arm using the FAS.

The following secondary endpoints are continuous endpoints with a single postbaseline timepoint and will be analyzed using an ANCOVA model. The model will include TAK-101 treatment dose group, schedule and stratification factor as fixed effects, and baseline measurement as covariate. Missing endpoint values will be imputed by multiple imputation.

- Change in CDSD v2.1 (24-Hour Recall) 3-day average score from baseline to Day 20.
- Change in CDSD v2.1 (24-Hour Recall) peak score from baseline to Day 20.
- Change from pre- to 4 hours post 12 g gluten challenge in IL-2 at Day 15.

The following secondary endpoints are continuous longitudinal endpoints and will be analyzed by mixed model for repeated measures approach. The model will include fixed effects for the TAK-101 treatment group, visit, treatment–by–visit interaction, the randomization stratification factor as fixed effects, and with the baseline measurement as a covariate. An unstructured (co)variance structure will be used to model the within-subject errors. The point estimates for the treatment difference from placebo and the 95% CI will be provided for the difference between each arm of TAK-101 versus placebo at Weeks 8, 14, and 20. Missing values will not be imputed.

- Change in CDSD v2.1 (24-Hour Recall) 3-day average score from baseline to Weeks 8, 14, and 20.
- Change in CDSD v2.1 (24-Hour Recall) peak score from baseline to Weeks 8, 14, and 20.
- Changes from pre- to 4 hours (using the peak score of either the 2- or 4-hour post gluten challenge) post single-day 3 g gluten challenge in IL-2 and CDSD v2.1 (Short Recall) at Weeks 8, 14, and 20.

Descriptive statistics will also be used to summarize all of the secondary endpoints at each visit.

The dose-response relationship will be characterized by change from baseline in IFN-γ ELISpot SFUs, IL-2, and symptoms at Day 20, and change in tetramer positive T cells before and after 6-day gluten challenge.

Exploratory Analyses:

The exploratory endpoints will be summarized descriptively by treatment group and visit. The patient-reported outcome (PRO) endpoints of PGIS (24-Hour and Short Recall versions), CDSD v2.1 (24-Hour and Short Recall versions), and CeD GSRS will also be descriptively summarized at the item level as applicable.

13.1.4 PK Analysis

Measured plasma concentrations of gliadin over time will be summarized descriptively using the PK analysis set. Individual concentration data versus time will be presented in a data listing. Further analysis may be performed as deemed necessary and will be reported separately from the CSR.

13.1.5 Biomarker Analysis

Analyses of biomarker endpoints are described as part of the efficacy analysis in Section 13.1.3.

13.1.6 Safety Analysis

Safety endpoints will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Change from baseline in clinical laboratory tests and vital signs will be summarized descriptively by treatment group. Subjects with markedly abnormal values for laboratory tests and vital signs will be summarized and listed.

13.1.7 Other Analyses

Additional analyses for PRO validation will be analyzed separately. A separate report will be created.

13.2 Interim Analysis and Criteria for Early Termination

An external DMC will be set up to review the safety data regularly and ad hoc during the course of the study. Safety information will be presented by treatment group to the DMC. The safety information to be presented includes AEs and abnormal laboratory values, with a focus on liver injury and IRs. The DMC will provide recommendations about stopping or continuing the study or treatment groups, including initiation of the second study cohort. To make the recommendation to start the second cohort, the DMC will be reviewing the first 30 subjects in the first cohort who have completed Visit 5 liver tests or have early terminated by Visit 5; data on liver enzyme elevation will be presented by treatment group. The DMC may also request additional analyses if they are deemed necessary to make a recommendation.

The DMC will also review the Day 20 activity data (ELISpot IFN-γ SFUs) from all subjects in the first study cohort and will make the recommendation on whether to enroll subjects in the 1 mg/kg dose group.

To maintain the integrity of the study, the interim safety analysis will be performed by an unblinded, independent statistical team who are separate from the study team (ie, individuals responsible for the conduct of the study). The study team, subjects, and investigators will remain blinded until final database lock.

13.3 Determination of Sample Size

The planned sample size is 108 subjects based on IFN-γ ELISpot assay data (IFN-γ SFUs) seen in previous analogous CeD studies (TGLIA-5.002). Assuming an 80% probability that the Day 20 IFN-γ SFU change from baseline in the placebo group is greater than that of the highest dose arm of TAK-101 (ie, 2 infusions of 4 mg/kg), a sample size of 90 subjects (15 subjects per arm) will have 80% power to detect a difference in the distribution for the primary endpoint between the highest dose arm of TAK-101 and the placebo arm. The 2-sided statistical hypothesis will be tested using the Wilcoxon rank-sum test and 0.05 significance level. To account for an assumed dropout rate of 17%, approximately 108 subjects will be randomized (18 subjects per arm).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study 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 will guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study 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, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). 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 study assessment.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study 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 study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the UK Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator will guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study 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 ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study 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 B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs 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. If any member of the IRB has direct participation in this study, 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 due to 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 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 for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site/ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification/drug no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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 study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB 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 and sponsor.

15.2 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 study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, 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 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 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. 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 study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, 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 study. 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 subject entering into the study; 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.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject 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 the monitor or the sponsor's designee, 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 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 study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

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).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

The sponsor may publish any data and information from the study (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 study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 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, Takeda 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 study, as defined in Takeda Policy/Standard. Takeda 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, Takeda will assist callers in locating study 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.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study 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 study insurance against the risk of injury to study subjects. Refer to the study 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.

16.0 REFERENCES

1. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut 2013;62(1):43-52.
2. Shan L, Molberg O, Parrot I, Hausch F, Filiz F, Gray GM, et al. Structural basis for gluten intolerance in celiac sprue. Science 2002;297(5590):2275-9.

3. Han A, Newell EW, Glanville J, Fernandez-Becker N, Khosla C, Chien YH, et al. Dietary gluten triggers concomitant activation of CD4+ and CD8+ alphabeta T cells and gammadelta T cells in celiac disease. Proc Natl Acad Sci U S A 2013;110(32):13073-8.
4. Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM, et al. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology 1998;115(3):551-63.
5. Mohamed BM, Feighery C, Kelly J, Coates C, O'Shea U, Barnes L, et al. Increased protein expression of matrix metalloproteinases -1, -3, and -9 and TIMP-1 in patients with gluten-sensitive enteropathy. Dig Dis Sci 2006;51(10):1862-8.
6. Leffler D. Celiac disease diagnosis and management: a 46-year-old woman with anemia. JAMA 2011;306(14):1582-92.
7. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac Disease and Nonceliac Gluten Sensitivity: A Review. JAMA 2017;318(7):647-56.
8. Lionetti E, Gatti S, Pulvirenti A, Catassi C. Celiac disease from a global perspective. Best Pract Res Clin Gastroenterol 2015;29(3):365-79.
9. Gibert A, Kruizinga AG, Neuhold S, Houben GF, Canela MA, Fasano A, et al. Might gluten traces in wheat substitutes pose a risk in patients with celiac disease? A population-based probabilistic approach to risk estimation. Am J Clin Nutr 2013;97(1):109-16.
10. Catassi C, Fabiani E, Iacono G, D'Agate C, Francavilla R, Biagi F, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. Am J Clin Nutr 2007;85(1):160-6.
11. Garber ME, Saldanha A, Parker JS, Jones WD, Kaukinen K, Laurila K, et al. A B-Cell Gene Signature Correlates With the Extent of Gluten-Induced Intestinal Injury in Celiac Disease. Cell Mol Gastroenterol Hepatol 2017;4(1):1-17.
12. Leffler D, Schuppan D, Pallav K, Najarian R, Goldsmith JD, Hansen J, et al. Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. Gut 2013;62(7):996-1004.
13. Vader W, Stepniak D, Kooy Y, Mearin L, Thompson A, van Rood JJ, et al. The HLA-DQ2 gene dose effect in celiac disease is directly related to the magnitude and breadth of gluten-specific T cell responses. Proc Natl Acad Sci U S A 2003;100(21):12390-5.
14. Caminero A, McCarville JL, Galipeau HJ, Deraison C, Bernier SP, Constante M, et al. Duodenal bacterial proteolytic activity determines sensitivity to dietary antigen through protease-activated receptor-2. Nat Commun 2019;10(1):1198.
15. Lebwohl B, Michaelsson K, Green PH, Ludvigsson JF. Persistent mucosal damage and risk of fracture in celiac disease. J Clin Endocrinol Metab 2014;99(2):609-16.
16. Lebwohl B, Granath F, Ekbom A, Smedby KE, Murray JA, Neugut AI, et al. Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: a population-based cohort study. Ann Intern Med 2013;159(3):169-75.
17. Hall NJ, Rubin GP, Charnock A. Intentional and inadvertent non-adherence in adult coeliac disease. A cross-sectional survey. Appetite 2013;68:56-62.

18. Costa AF, Sugai E, Temprano MP, Niveloni SI, Vazquez H, Moreno ML, et al. Gluten immunogenic peptide excretion detects dietary transgressions in treated celiac disease patients. World J Gastroenterol 2019;25(11):1409-20.
19. Moreno ML, Cebolla A, Munoz-Suano A, Carrillo-Carrion C, Comino I, Pizarro A, et al. Detection of gluten immunogenic peptides in the urine of patients with coeliac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing. Gut 2017;66(2):250-7.
20. Comino I, Fernandez-Banares F, Esteve M, Ortigosa L, Castillejo G, Fambuena B, et al. Fecal gluten peptides reveal limitations of serological tests and food questionnaires for monitoring gluten-free diet in celiacdisease patients. Am J Gastroenterol 2016;111(10):1456-65.
21. Syage JA, Kelly CP, Dickason MA, Ramirez AC, Leon F, Dominguez R, et al. Determination of gluten consumption in celiac disease patients on a gluten-free diet. Am J Clin Nutr 2018;107(2):201-7.
22. Lerner BA, Phan Vo LT, Yates S, Rundle AG, Green PHR, Lebwohl B. Detection of gluten in gluten-free labeled restaurant food: Analysis of crowd-sourced data. Am J Gastroenterol 2019.
23. Silvester JA, Comino I, Kelly CP, Sousa C, Duerksen DR, DOGGIE BAG Study Group. Most patients with celiac disease on gluten-free diets consume measurable amount of gluten. Gastroenterology 2019;19:48945-8.
24. Getts DR, Shea LD, Miller SD, King NJ. Harnessing nanoparticles for immune modulation. Trends Immunol 2015;36(7):419-27.
25. Getts DR, Turley DM, Smith CE, Harp CT, McCarthy D, Feeney EM, et al. Tolerance induced by apoptotic antigen-coupled leukocytes is induced by PD-L1+ and IL-10-producing splenic macrophages and maintained by T regulatory cells. J Immunol 2011;187(5):2405-17.
26. Regev A, Seeff LB, Merz M, Ormarsdottir S, Aithal GP, Gallivan J, et al. Causality assessment for suspected DILI during clinical phases of drug development. Drug Saf 2014;37 Suppl 1:S47-56.

Appendix A Schedule of Study Procedures

Table 16.a Schedule of Study Procedures

	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Early Termination
	Visit 1	Visit 2 [a]	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Visit 6	Visit 7 [a]	Visit 8 [a]	Visit 9 [a] (EOS)	ET
Day	-42 to -21	-41 to -14	1	3 ± 1	8	10 ± 1	15	20	57 ± 4	99 ± 6	141 ± 6	
	Week -6	Week -6 to -2	Week 0		Week 1		Week 2	Week 3	Week 8	Week 14	Week 20	30 days after last dose
Assessment												
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Hepatitis/HIV screening	X											
Medical history [b]	X											
Medication history	X	X	X		X		X	X	X	X	X	X
Physical examination	X		X		X				X	X	X	X
Vital signs [c]	X	X	X		X		X	X	X	X	X	X
Randomization			X									
PTE/AE assessment	X	X	X		X		X	X	X	X	X	X
Electrocardiogram	X											
Concomitant medications	X	X	X		X		X	X	X	X	X	X
Clinical laboratory evaluations (hematology, liver tests, and chemistry) [d]	X	X	X		X		X	X	X	X	X	X
Liver tests only [e]				X		X						
Urinalysis	X		X								X	X
Pregnancy test (hCG) [f]	X		X		X		X	X	X	X	X	X
Urine drug and alcohol screening [g]	X											
Blood sample for HLA typing	X											
Celiac serologies [h]	X		X		X		X	X	X		X	X
Randomization			X									
Study treatment infusion			X		X [i]							
Gluten challenge [j]		X					<----- X [k] ------>		X	X	X	
Blood sample for immunophenotyping, tetramer staining, and ELISpot [l]			X				X	X				

Table 16.a Schedule of Study Procedures

	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Early Termination
	Visit 1	**Visit 2 [a]**	**Visit 3**	**Visit 3.a**	**Visit 4**	**Visit 4.a**	**Visit 5**	**Visit 6**	**Visit 7 [a]**	**Visit 8 [a]**	**Visit 9 [a] (EOS)**	**ET**
Day	**-42 to -21**	**-41 to -14**	**1**	**3 ± 1**	**8**	**10 ± 1**	**15**	**20**	**57 ± 4**	**99 ± 6**	**141 ± 6**	
	Week -6	**Week -6 to -2**	**Week 0**		**Week 1**		**Week 2**	**Week 3**	**Week 8**	**Week 14**	**Week 20**	**30 days after last dose**
Plasma sample for protein [m]	X	X	X				X	X	X	X	X	
Blood sample for RNA [m]	X	X	X				X	X	X	X	X	
Serum sample for immunogenicity [n]	X		X		X		X		X	X	X	X
Sampling for complement [o]			X		X		X				X	X
Sampling for CRS [o]			X		X		X					
Sampling for tryptase and histamine [p]					X							
Plasma sample for gliadin PK [o]			X		X							
Urine sample for gluten	X	X	X		X		X	X	X	X	X	X
CDSD v2.1 (24-Hour Recall) [q]		<----------X---------->										
CDSD v2.1 (Short Recall) [r]		X					X		X	X	X	
PGIS (24-Hour Recall) [s]	X	X	X				X	X	X	X	X	X
PGIS (Short Recall) [t]		X					X		X	X	X	
CeD GSRS [u]	X		X				X	X			X	
Additional exploratory questions [v]		X					X	X	X	X	X	

ADA: antidrug antibody; AE: adverse event; CDSD v2.1: Celiac Disease Symptom Diary Version 2.1; CeD: celiac disease; COVID-19: coronavirus disease 2019; CRS: cytokine release syndrome; DGP: deamidated gliadin peptide; ELISpot: enzyme-linked immunospot; EOS: end of study; ET: early termination; GSRS: Gastrointestinal Symptom Rating Scale; hCG: human chorionic gonadotropin; IL-2: interleukin-2; IR: infusion reaction; PGIS: Patient Global Impression Of Severity; PK: pharmacokinetic; PT: prothrombin time; PTE: pretreatment event; PTT: partial thromboplastin time; tTG: tissue transglutaminase.

[a] Visits 2, 7, 8, and 9 can occur in the clinic or at home.

[b] Medical history will include the Gluten-Free Eating Assessment Tool.

[c] Vital signs will be obtained before dosing and at 15, 30, and 60 min after the start of treatment infusion; immediately at the end of infusion; and 1 hour after the end of infusion. After 1 hour, if vital signs are stable, the subject may be discharged at the discretion of the investigator.

[d] Hematology tests to include platelet count and coagulation tests (D-dimer, PT, PTT, fibrinogen). Serologic or direct viral testing for COVID-19 may be performed according to site guidance and/or at the discretion of the investigator.

[e] Liver tests will be measured 2 days (±1) after each study treatment infusion (may be performed at home or in clinic). Liver enzymes/bilirubin must be confirmed to be ≤1.2 × ULN

Table 16.a Schedule of Study Procedures

	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Early Termination
	Visit 1	Visit 2 [a]	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Visit 6	Visit 7 [a]	Visit 8 [a]	Visit 9 [a] (EOS)	ET
Day	-42 to -21	-41 to -14	1	3 ± 1	8	10 ± 1	15	20	57 ± 4	99 ± 6	141 ± 6	
	Week -6	Week -6 to -2	Week 0		Week 1		Week 2	Week 3	Week 8	Week 14	Week 20	30 days after last dose

before the second dose is administered.
[f] Serum pregnancy test at Visit 1; all others are urine pregnancy tests.
[g] Positive results will be assessed by the investigator, and exclusion will be based on local regulations and subject's medical history. Positive cases should be discussed with the medical monitor.
[h] IgG DGP, IgA DGP, and IgA tTG. On drug/placebo dosing days, samples should be collected before dosing.
[i] Second infusion may be delayed up to 2 days if liver test results are pending.
[j] All subjects will undergo a single-day 3 g gluten challenge administered at the site of blood testing, either in the clinic or at home during run-in (Weeks -6 to -2). Where possible, the gluten challenge at run-in should be performed after subjects have met study criteria for laboratory testing performed at screening (Visit 1). Single-day 3 g gluten challenges will be administered at the site of blood testing, either in the clinic or at home at Weeks 8, 14, and 20 to assess persistence of response to therapy. There will be a minimum washout period of 2 weeks between gluten challenges.
[k] On Day 15 of the 6-day gluten challenge, subjects will consume gluten in the clinic, on Days 16 through 19, subjects will consume gluten at home, and on Day 20 of the 6-day gluten challenge subjects will consume gluten at home or at the clinic. See the Schedule of Study Procedures for 6-Day At-Home Gluten Challenge for more details.
[l] Testing to be done before dosing at Week 0 and before gluten challenge at Week 2, and also after gluten challenge at Day 20/Week 3.
[m] IL-2 levels and RNA sampling will be tested before and 4 hours after each single-day gluten challenge at run-in, on Weeks 8, 14, and 20 and before and 4 hours after the first dose of the 6-day challenge (Week 2).
[n] Collect serum sample for ADA before dosing at Weeks 0 and 1 and before gluten challenge at Week 2, 8, 14, and 20.
[o] Samples should be taken predose (within 30 minutes of dosing), 30 minutes after start of the infusion, and at end of infusion on each study treatment visit (Weeks 0 and 1), and before gluten challenge at Week 2 (complement and CRS sampling only). Samples for CRS and complement should also be collected at the time of an IR.
[p] Collect samples for tryptase (serum) and histamine (plasma) before and at the end of the second study treatment infusion.
[q] CDSD v2.1 24-Hour Recall is to be completed daily by the subject for the duration of the study.
[r] CDSD v2.1 (Short Recall) is to be completed immediately before initiation of all gluten challenges (single-day and 6-day). It is also to be completed 2 hours and 4 hours after each of the single-day 3 g gluten challenges, and 2 hours and 4 hours after the first dose of the 6-day gluten challenge.
[s] The PGIS (24-Hour Recall) is to be administered before any other scheduled procedure. During run-in, the PGIS (24-Hour Recall) will be administered on the day immediately before and within 24 hours after gluten challenge.
[t] PGIS (Short Recall) is to be completed immediately before initiation of all gluten challenges (single-day and 6-day). It is also to be completed 2 hours and 4 hours after each of the single-day 3 g gluten challenges, and 2 hours and 4 hours after the first dose of the 6-day gluten challenge.
[u] CeD GSRS is to be completed before the gluten challenge on Day 15 and within 24 hours or on the day immediately after completion of the gluten challenge on Day 20.
[v] Additional exploratory questions are to be administered immediately after the PGIS (Short Recall) if administered. Otherwise administered immediately after the PGIS (24-Hour Recall).

Table 16.b Schedule of Study Procedures for 6-Day At-Home Gluten Challenge

Follow-up Period						
	Visit 5					**Visit 6**
Day	**15**	**16**	**17**	**18**	**19**	**20**
	Week 2					**Week 3**
Assessment						
Home gluten challenge [a]		X	X	X	X	X
Home gluten challenge daily diary		X	X	X	X	X
Urine sample for gluten [b]	X		X [c]			X
PGIS (24-Hour Recall) [d]	X	X	X	X	X	X
Additional exploratory questions [e]	X	X	X	X	X	X

CDSD v2.1: Celiac Disease Symptom Diary Version 2.1; PGIS: Patient Global Impression Of Severity.

[a] Day 15 gluten challenge will be completed in the clinic. Day 16-19 gluten challenge will be completed at home. Day 20 gluten challenge may be completed at home or at the clinic.

[b] Urine samples for assessment of gluten exposure will be collected in the clinic on Day 15 of the 6-day gluten challenge (predose), Day 17 at home (first morning void), and Day 20 at home or in clinic (first morning void) (predose).

[c] The Day 17 urine sample should be stored (refrigerated or frozen) and brought to the clinic on Visit 6, Day 20.

[d] PGIS (24-Hour Recall) is to be administered immediately before the CDSD v2.1 (24-Hour Recall) during the 6-day gluten challenge (Days 15-20).

[e] Additional exploratory questions are to be administered immediately after the CDSD v2.1 (24-Hour Recall) during the 6-day gluten challenge (Days 15-20).

Appendix B 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 study.

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB. 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 study. 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.
9. Prepare and maintain adequate case histories of all persons entered into the study, 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.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

1. A statement that the study 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 study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
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, 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 study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB 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 study.
22. A statement that results of pharmacogenomic 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 study 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 study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:

    b) 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) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;

    c) 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, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    d) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    e) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

    f) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 60 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued, and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 120 days after last dose. If the partner of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical study information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda 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 UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs.

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

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study 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 Takeda and other parties for the purposes described above.

Appendix E Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up

Investigators must be vigilant for abnormal liver test results in subjects during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical trial subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver test results in clinical study subjects who had no known liver disease and had either normal or near normal baseline liver test results (ie, ALT <2 × ULN, total bilirubin <1.5 × ULN, and ALP <1.5 × ULN) at the time of enrollment.

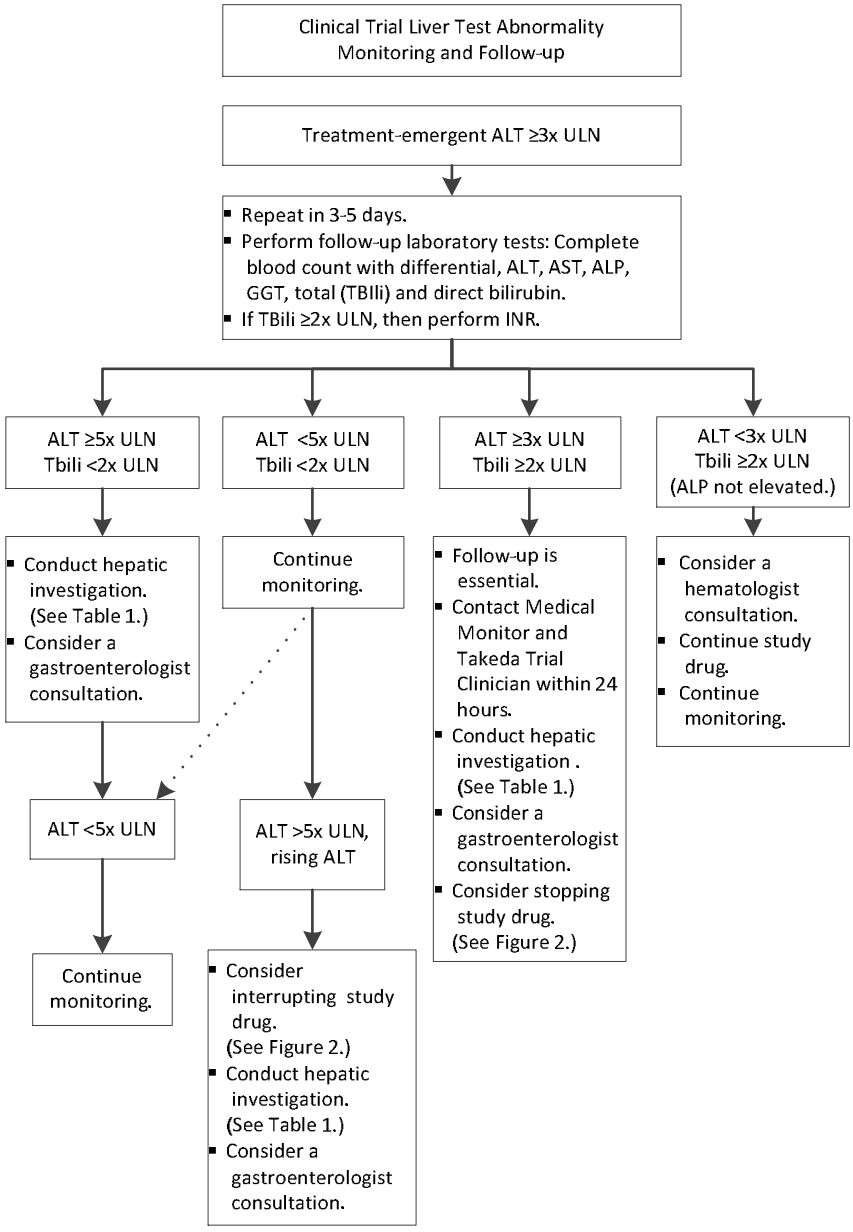
In evaluating trial subjects with abnormal liver test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 1. Suggested hepatic investigations are listed in Table 1.

Liver enzymes must be assessed in all subjects after the first infusion and confirmed to be within acceptable range before receiving the second infusion. To be eligible for the second study drug infusion, post-first infusion liver enzymes must be confirmed to be ≤1.2 × ULN.

Subjects with Combined Elevations in Aminotransferase and Bilirubin

If a subject has elevated ALT ≥3 × ULN with concurrent elevated total bilirubin ≥2 × ULN ***or*** elevated INR >1.5, the investigator must contact the Medical Monitor and Takeda Trial Clinician within 24 hours. Hepatic investigations as suggested in Table 1 should be initiated. Any event of elevated ALT ≥3 × ULN with concurrent elevated total bilirubin ≥2 × ULN ***or*** elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

Appendix E Figure 1: Liver Test Abnormality Monitoring and Follow-up



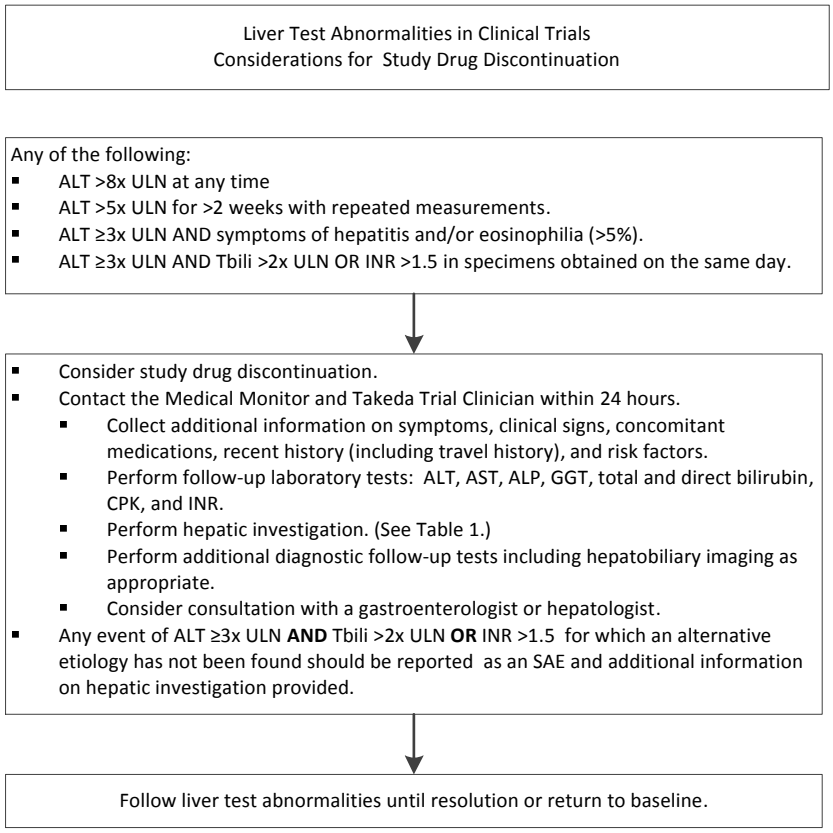
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Appendix E Table 1: Hepatic Investigation

Medical History	• Concomitant medications (including OTC medications, such as acetaminophen, and herbal supplements). • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). • Alcohol intake. • Hepatobiliary disorder. • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia). • Travel history.
Physical Examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting. • Right upper quadrant pain or tenderness, fever, jaundice, rash. • Eosinophilia >5%.
Hepatic/Hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	• Hepatitis A antibody (total and IgM). • Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (anti-HBs), Hepatitis B core antibody (IgM anti-HBc), Hepatitis C antibodies (anti-HCV). • Hepatitis E (IgG and IgM). • Consider PCR for Hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen [VCA] nuclear antigen [EBNA], early antigen [EA]). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	• Anti-nuclear antibody (ANA). • Anti-smooth muscle antibody (ASMA). • Anti-liver-kidney microsomal antibody (anti-LKM).

OTC: over-the-counter; PCR: polymerase chain reaction.

Appendix E Figure 2: Liver Test Abnormalities: Considerations for Study Drug Discontinuation



ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Appendix F CDSD Version 2.1 (24-Hour Recall)

Instructions:

Welcome to the Celiac Disease Symptom Diary. Please complete this diary each evening before you go to bed. The diary asks about your celiac symptoms at their worst during the past 24 hours.

1. During the past 24 hours, how severe was your diarrhea at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

2. During the past 24 hours, how severe was your abdominal (belly) pain at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

3. During the past 24 hours, how severe was your bloating (feeling as if you need to loosen your clothes) at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

4. During the past 24 hours, how severe was your nausea (feeling as if you were going to vomit or throw up) at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

5. During the past 24 hours, how severe was your tiredness at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

Episodes Bowel Movements, Diarrhea, and Vomiting

6. How many times did you vomit (throw up) in the past 24 hours? (Please count each time you vomited rather than the number of trips to the bathroom). ____

7. How many bowel movements (poops) did you have in the past 24 hours? ____

8. How many of those bowel movements (poops) looked like type 6 or 7 in the picture below? ____

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, mushy stool
Type 7		Watery, no solid pieces. ENTIRELY LIQUID

Appendix G CDSD Version 2.1 (Short Recall)

Instructions:

Welcome to the celiac disease symptom diary. The diary asks about your celiac symptoms during the gluten challenge. You will be asked to answer this questionnaire prior to the gluten challenge for your symptoms in the past 2 hours. After your gluten challenge you will be asked to answer this questionnaire every 2 hours. Please answer these questions about your symptoms during the time since you last answered this questionnaire (approximately 2 hours ago).

1. During the past 2 hours, how severe was your diarrhea at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

2. During the past 2 hours, how severe was your abdominal (belly) pain at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

3. During the past 2 hours, how severe was your bloating (feeling as if you need to loosen your clothes) at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

4. During the past 2 hours, how severe was your nausea (feeling as if you were going to vomit or throw up) at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

5. During the past 2 hours, how severe was your tiredness at its worst?

   ☐ None

   ☐ Mild

   ☐ Moderate

   ☐ Severe

   ☐ Very severe

Episodes Bowel Movements, Diarrhea, and Vomiting

6. How many times did you vomit (throw up) in the past 2 hours? (Please count each time you vomited rather than the number of trips to the bathroom). ____

7. How many bowel movements (poops) did you have in the past 2 hours? ____

8. How many of those bowel movements (poops) looked like type 6 or 7 in the picture below? ____

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, mushy stool
Type 7		Watery, no solid pieces. ENTIRELY LIQUID

Appendix H CeD GSRS

This survey contains questions about how you have been feeling and what it has been like during the past week. Mark the choice that best applies to you and your situation with an "X" in the box.

1. Have you been bothered by PAIN OR DISCOMFORT IN YOUR UPPER ABDOMEN OR THE PIT OF YOUR STOMACH during the past week?

   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

2. Have you been bothered by HUNGER PAINS in the stomach during the past week? (This hollow feeling in the stomach is associated with the need to eat between meals.)

   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

3. Have you been bothered by NAUSEA during the past week? (By nausea we mean a feeling of wanting to throw up or vomit.)

   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

4. Have you been bothered by RUMBLING in your stomach during the past week? (Rumbling refers to vibrations or noise in the stomach.)

   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

5. Has your stomach felt BLOATED during the past week? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)

   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

6. Have you been bothered by BURPING during the past week? (Burping refers to bringing up air or gas from the stomach via the mouth, often associated with easing a bloated feeling.)

   ☐ No discomfort at all

   ☐ Minor discomfort

   ☐ Mild discomfort

   ☐ Moderate discomfort

   ☐ Moderately severe discomfort

   ☐ Severe discomfort

   ☐ Very severe discomfort

7. Have you been bothered by PASSING GAS OR FLATUS during the past week? (Passing gas or flatus refers to the need to release air or gas from the bowel, often associated with easing a bloated feeling.)

   ☐ No discomfort at all

   ☐ Minor discomfort

   ☐ Mild discomfort

   ☐ Moderate discomfort

   ☐ Moderately severe discomfort

   ☐ Severe discomfort

   ☐ Very severe discomfort

8. Have you been bothered by DIARRHEA during the past week? (Diarrhea refers to a too-frequent emptying of the bowels.)

   ☐ No discomfort at all

   ☐ Minor discomfort

   ☐ Mild discomfort

   ☐ Moderate discomfort

   ☐ Moderately severe discomfort

   ☐ Severe discomfort

   ☐ Very severe discomfort

9. Have you been bothered by LOOSE STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being loose.)

   ☐ No discomfort at all
   ☐ Minor discomfort
   ☐ Mild discomfort
   ☐ Moderate discomfort
   ☐ Moderately severe discomfort
   ☐ Severe discomfort
   ☐ Very severe discomfort

10. Have you been bothered by an URGENT NEED TO HAVE A BOWEL MOVEMENT during the past week? (This urgent need to go to the toilet is often associated with a feeling that you are not in full control.)

    ☐ No discomfort at all
    ☐ Minor discomfort
    ☐ Mild discomfort
    ☐ Moderate discomfort
    ☐ Moderately severe discomfort
    ☐ Severe discomfort
    ☐ Very severe discomfort

Appendix I PGIS Version 1.1 (24-Hour Recall)

Please complete the following question. Please choose only 1 answer.

Overall, how would you rate your symptoms related to celiac disease during the last 24 hours?

- ☐ No symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Appendix J PGIS Version 1.1 (Short Recall)

Please complete the following question. Please choose only 1 answer.

Overall, how would you rate your symptoms related to celiac disease during the last 2 hours?

- ☐ No symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Appendix K Additional Exploratory Questions

In the past 2 hours, how severe was your irritability at its worst?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

In the past 2 hours, how severe was your "brain fog" at its worst?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Appendix L NCI CTCAE Grading

Injury, Poisoning, and Procedural Complications

NCI CTCAE Term	
Infusion related reaction [a]	
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.
Grade 3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death.

IV: intravenous; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID: nonsteroidal anti-inflammatory drug.

[a] A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of TAK-101 for the Prevention of Gluten-Specific T Cell Activation in Subjects with Celiac Disease on a Gluten-Free Diet

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
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Liu, Pengyu	Biostatistics Approval	12-Jun-2020 08:17 UTC
Sun, Wan	Clinical Pharmacology Approval	12-Jun-2020 16:50 UTC