Clinical Study Protocol

NCT Number: NCT04530123

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

Study Number: TAK-101-2001

Document Version and Date: Amendment 03, 19 Jul 2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

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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. 500 Kendall Street, Cambridge, MA 02142
Study Number:	TAK-101-2001
IND Number:	017579
EU CT Number:	Not Applicable
NCT Number:	NCT04530123
Compound:	TAK-101
Date:	19 July 2024
Version/Amendment Number:	3

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Amendment History:

Date	Amendment Number	Amendment Type	Region
19 July 2024	Amendment 3	Substantial	Global
09 November 2023	Amendment 2	Substantial	Global
02 December 2021	Amendment 1	Substantial	Global
11 June 2020	Initial version	Not Applicable	Global

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This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

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
Adverse event of special interest, 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)	[redacted], MD, MS, AGAF [redacted], Clinical Science Office Telephone: [redacted] Mobile: [redacted]
Sponsor Trial Clinician	[redacted], Pharm D, MS. [redacted], Clinical Science Office/Mobile: [redacted]

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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 Council 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.

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[redacted], Pharm D, MS. Date
[redacted], Clinical Science

[redacted], MS Date
[redacted], Statistical and Quantitative Sciences

[redacted], PhD Date
[redacted],
Quantitative Clinical Pharmacology,
Data Sciences Institute

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 Council 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.

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Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 3 Summary of Changes

Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reason for this amendment is to address substantial changes as noted below:

- Update dosage nomenclature for TAK-101 in concordance with current manufacturing process and release specifications and to align globally across countries' new nomenclature.
- Update in sample size.
- Update in cohort groups.
- Update in independent data monitoring committee assessment criteria and addition of an optional internal interim analysis.
- Update assessment and management of potential adverse events, particularly allergic reactions.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Throughout	Updated the dosing nomenclature from mg/kg PLGA NP to µg/kg GE at all applicable places. • 1 mg/kg PLGA NP to 12.5 µg/kg GE • 2 mg/kg PLGA NP to 25 µg/kg GE • 4 mg/kg PLGA NP to 50 µg/kg GE • 8 mg/kg PLGA NP to 100 µg/kg GE • 500 mg PLGA NP 6250 µg GE	To update in concordance with current manufacturing process and release specifications and align globally across countries.
2.	Title page	Updated sponsor address.	Administrative change
3.	Title page	Added the NCT number.	Administrative change
4.	Title page, Section 2.0 STUDY SUMMARY	Updated "EudraCT Number" to "EU CT Number."	Administrative change
5.	Title page, Section 4.1.4 Summary of Nonclinical Findings, Section 7.2 Exclusion Criteria	Removed TIMP or TIMP-GLIA.	Administrative change

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6.	Section 1.1 Contacts	Updated the designation of "responsible medical officer" and added "sponsor trial clinician."	Administrative change
7.	Section 1.2 Approval	Updated study signatories for Statistical and Quantitative Sciences, Clinical Science, and Quantitative Clinical Pharmacology.	Administrative change
8.	Section 2.0 STUDY SUMMARY: Study Design, Number of Subjects, Sample Size Justification Section 6.1 Study Design Section 13.2 Determination of Sample Size	Updated the sample size from approximately 108 subjects to approximately 90 subjects after removal of 2 of 3 single-infusion dose arms.	Changes to study design based on interim non-clinical data suggesting more robust activity with 2 infusion doses.
9.	Section 2.0 STUDY SUMMARY: Study Design, Number of Subjects Section 6.1 Study Design	Updated study Cohort 2 sample size to be: • Up to 45 subjects if it is decided to include both TAK-101 50 µg/kg GE and 12.5 µg/kg GE dose levels, or • Up to 27 subjects if it is decided to include only the TAK-101 12.5 µg/kg GE dose level and not 50 µg/kg GE.	Changes in study design based on interim nonclinical data review suggesting more robust activity with 2 infusion doses as per change No. 8.
10.	Section 2.0 STUDY SUMMARY: Study Design, Dose Level(s) Section 6.1 Study Design Table 6.a Dose and Regimen Table 8.a Dose and Regimen	• Study groups re-numbered and re-described to reflect that: • Group D will receive 50 µg/kg GE TAK-101 for all 3 doses. • Group E will receive placebo for the first 2 doses and 12.5 µg/kg GE TAK-101 for the third dose. • Group F will receive 12.5 µg/kg GE TAK-101 for all 3 doses. • All other groups are removed.	Changes in study design based on interim non-clinical data suggesting more robust activity with 2 infusion doses as per change No. 8.
11.	Section 2.0 STUDY SUMMARY: Study Design Section 6.1 Study Design	Added below text: HLA distribution will be monitored throughout the study and enrollment of subjects in certain strata may be limited in order to reflect the known distribution of HLA types in the celiac disease (CeD) population.	Added to ensure ability to generalize study population and study results to overall CeD population.

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12.	Section 2.0 STUDY SUMMARY: Study Design	Added following text: "For the third dose, all randomized subjects will receive the same dose of TAK-101 that they received with initial treatment, and all subjects initially randomized to placebo will receive 25 µg/kg GE TAK-101 or 12.5 µg/kg GE TAK-101, if it is decided not to include the 50 µg/kg GE dose level in Cohort 2."	For consistency.
13.	Section 2.0 STUDY SUMMARY: Study Design	Updated "Subjects will be observed for treatment-emergent adverse events (TEAEs), including infusion-related reactions (IRR) for up to 2 hours following each study drug infusion" to "Subjects will be observed for treatment-emergent adverse events (TEAEs), including infusion-related reactions (IRRs), potential allergic reactions, and drug-induced cytokine release syndrome (CRS), for 2 hours following each study drug infusion."	For consistency.
14.	Section 2.0 STUDY SUMMARY: Study Design Section 6.1 Study Design	Updated text regarding samples collected for safety-related endpoints.	To streamline.
15.	Section 2.0 STUDY SUMMARY	[redacted]	Alignment with sponsor protocol templates
16.	Section 2.0 STUDY SUMMARY	Updated HLA-DQ2 to HLA-DQ2.5 in primary objective and applicable places.	Clarification
17.	Section 2.0 STUDY SUMMARY	Updated estimated number of study sites to approximately 58.	Update based on operational strategy.
18.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	Updated the first secondary objective to: • Evaluate the safety and tolerability of TAK-101.	Clarification
19.	Section 2.0 STUDY SUMMARY: Route of Administration Section 8.1.3 Dose and Regimen	Updated infusion time to approximately 2 hours. Updated the escalating rates under Section 8.1.3.	Correction and updated to align timings when patient vital signs are being checked.
20.	Section 2.0 STUDY SUMMARY: Main Criteria	Added text for allowing the enrollment of subjects with Gilbert's syndrome	Clarification

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	for Exclusion Section 7.2 Exclusion Criteria	with total bilirubin >1.5 × the Upper limit of normal (ULN)	
21.	Section 2.0 STUDY SUMMARY: Main Criteria for Exclusion Section 7.2 Exclusion Criteria	Updated and simplified the text for exclusion criteria for coronavirus disease-2019 (COVID-19) infection.	Clarification
22.	Section 2.0 STUDY SUMMARY: Statistical Considerations Section 13.1.3 Efficacy Analysis	Removed the following from multiplicity testing: TAK-101 4 mg/kg 1 infusion versus placebo. TAK-101 1 mg/kg 1 infusion versus placebo.	Changes in study design based on interim nonclinical data suggesting more robust activity with 2 infusion doses as per change No. 8.
23.	Section 2.0 STUDY SUMMARY: Secondary Endpoints Section 5.2.2 Secondary Endpoints	Updated 7 secondary endpoints as below: • Safety and tolerability as assessed by TEAEs, AESIs, physical examinations, vital signs, and clinical laboratory testing, including liver tests. • Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day average nausea severity score measured in Celiac Disease Symptom Diary version 2.1 (CDSD v2.1, 24-Hour Recall). • Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall). • Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20. • Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at each of the following time points: run-in (Visit 2), Day 15,	To allow more complete pre-specified analyses of immunologic and patient-reported data

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		and Weeks 8, 14, and 20. • Plasma concentration of TAK-101 on dosing days. • Serum concentration of antidrug antibodies (ADAs) to various doses of TAK-101 (deamidated gliadin peptide [DGP]- immunoglobulin G [IgG]). Note: Changes in run-in (Visit 2) and Weeks 8, 14, and 20 will be calculated using the difference of average scores.	
24.	Section 2.0 STUDY SUMMARY: Secondary Endpoints Section 5.2.2 Secondary Endpoints	Added a new secondary endpoint as below: • Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly gastrointestinal (GI) symptom severity score (CDSD v2.1, 24-Hour Recall).	To allow more complete prespecified analyses of patient-reported data.
25.	Section 2.0 STUDY SUMMARY: Statistical Considerations: Analysis Sets Section 13.1.1 Analysis Sets	Added definition of Randomized Analysis Set.	Clarification
26.	Section 2.0 STUDY SUMMARY: Statistical Considerations: Analysis Sets	Added definition of per protocol set (PPS).	Clarification
27.	Section 2.0 STUDY SUMMARY: Secondary Efficacy Analyses	Updated according to Section 13.1.3 Efficacy Analysis updates.	For consistency with correction and clarification of analysis plan.
28.	Section 2.0 STUDY SUMMARY: Interim Analysis	Added information for safety interim analysis (IA) and optional internal IA.	Clarification
29.	Section 4.1.2 Name and Description of Study Drug	Revised description of TAK-101 and added the mechanism of action figure for TAK-101.	Clarification
30.	Section 4.1.3 Purpose for New TAK-101 Dosage Nomenclature	Added new section and dosage nomenclature Table 4.a.	To align globally across countries.

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31.	Section 4.1.4 Summary of Nonclinical Findings	Revised the details for nonclinical studies.	Clarification and simplification.
32.	Section 4.1.4.1 Nonclinical Safety Summary	• Updated the subheading text from "Nonclinical Safety Findings" to "Nonclinical Safety Summary." • Removed subheadings In Vivo Pharmacology, Safety Pharmacology and the detailed information for safety pharmacology studies under it.	Clarification/stream-lining of information required for the protocol.
33.	Section 4.1.4.1 Nonclinical Safety Summary	• Removed subheading Single- and Repeat-Dose Toxicity. • Streamlined descriptions for toxicology studies. • Added summary for safety pharmacology toxicities of concern. • Removed the table for no-observed-adverse-effect level in GLP-Compliant Repeat-Dose Toxicity Studies. • Added details for 2-dose bridging study for manufacturing Process A and Process B.	Simplification and inclusion of text for newly completed nonclinical study.
34.	Section 4.1.4.1 Nonclinical Safety Summary	• Removed subheading Reproductive and Developmental Toxicity. • Removed study numbers for rats and rabbit studies and minor edits were done.	Clarification/Simplification.
35.	Section 4.1.5 Summary of Clinical Findings	• Updated study design details for Study # TGLIA-5.001 and Study # TGLIA-5.002. • Summarized information on AEs for both completed studies and added reference to IB Edition 5 for detailed safety data.	Clarification/Simplification of completed clinical studies.
36.	Section 4.3 Benefit/Risk Profile	Revised the detail for benefit and risk profile.	Update/Clarification
37.	Section 4.3.1 Risk Related to Oral Gluten Exposure	Updated from "promptly" to "within 48-72 hours" for any signs/symptoms of study-related gluten exposure to resolve and added minor edits.	Clarification

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38.	Section 4.3.1 Risk Related to Oral Gluten Exposure	Updated the "allergic reactions to wheat" from "risk" to "potential risk" and added minor edits.	Update/Clarification
39.	Section 5.2.3 Exploratory Endpoints	[redacted]	[redacted]
40.	Section 5.2.3 Exploratory Endpoints	[redacted]	[redacted]
41.	Section 6.1 Study Design	Adde following text: "In addition, the IDMC will review safety and laboratory data from the third infusions given to the first 5 subjects and, if needed, the IDMC will make recommendations as appropriate."	For Consistency.

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42.	Section 6.1 Study Design	Updated the "CRS" to "drug-induced CRS" for observation of TEAEs and added minor edits.	Clarification.
43.	Table 6.a Dose and Regimen Figure 6.b Schematic of Study Cohorts: Initial Dosing Regimens	Updated table and figure to reflect new study design and study groups.	Clarification.
44.	Section 6.1 Study Design	Added "The database will be locked when the last subject has completed all procedures and assessments or discontinued the study early. After final database lock, the study will be unblinded and a clinical study report will be prepared."	Consistency with Study Summary.
45.	Section 6.2 Justification for Study Design, Dose, and Endpoints	Additional justification for testing lower doses of TAK-101 in this study.	Clarification
46.	Section 6.3.1 Study Stopping Rules	Revised the criteria for study stopping.	Update/Clarification
47.	Section 7.1 Inclusion Criteria	Updated inclusion criterion No. 8 to include that the use of a barrier method of contraception should continue for 100 days after the last dose.	Clarification
48.	Section 7.1 Inclusion Criteria	Updated inclusion criterion No. 9 to include that the highly effective method of contraception should continue for 40 days after the last dose.	Clarification
49.	Section 2.0 STUDY SUMMARY: Main Criteria for Exclusion: Section 7.2 Exclusion Criteria	Updated exclusion criterion No. 5 to: Has known or suspected allergy to wheat such as hypersensitivity, and/or anaphylaxis including wheat-dependent exercise-induced anaphylaxis (WDEIA). If there is a possible history of urticaria, angioedema, or anaphylaxis to wheat, investigators should perform testing for wheat anti-IgE antibodies or refer to an allergist for evaluation prior to enrollment to rule out any of these allergies.	Clarification.
50.	Section 7.2 Exclusion Criteria	Updated exclusion of female subjects not willing to use study-recommended contraceptive measure (No. 11).	Clarification.

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	Appendix C	Duration for No. 26 was corrected as per exclusion criterion No. 12.	
51.	Section 2.0 STUDY SUMMARY: Main Criteria for Exclusion: Section 7.2 Exclusion Criteria	Updated exclusion criterion No. 20 to: "Has known allergy to or intolerance of TAK-101 or any of its ingredients or excipients (as referenced in Section 4.1.2). Also, any subject with a symptomatic allergic reaction that is confirmed by lab serology such as elevated tryptase levels (Refer to Appendix N) following the administration of TAK-101 will be excluded from future dosing."	Clarification.
52.	Section 7.3 Excluded Medications	Added "Subjects should not start new medications during the duration of the trial without approval of the medical monitor and/or sponsor unless these medications are urgently required per investigator's decision. If this is urgently necessary, please notify sponsor afterwards."	Clarification
53.	Section 7.4 Diet, Fluid, Activity Control and Treatment Facilities	Added below text: Updated details for gluten challenge administration with quantity for each day and the supply and consumption of gluten (challenge agent).	Clarification
54.	Section 7.5 Criteria for Discontinuation of Study Drug	Updated and added the criteria for discontinuation of study drug in case of allergic reaction/infusion-related reactions (IRRs)/liver findings.	Clarification
55.	Section 8.0 CLINICAL STUDY MATERIAL MANAGEMENT	Added reference to pharmacy manual.	Clarification.
56.	Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling	Removed the subheadings "Challenge Agents" and "Sponsor-Supplied Drugs" and the text underneath, with incorporating text in Section 7.4.	Clarification and simplification
57.	Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling	Removed reference in pharmacy manual for placebo dosage form, strengths, composition etc and added minor edits.	Correction

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58.	Section 8.1.1.3 Rescue Medications	Added text to specify that rescue medications will be those used for "symptoms associated with the gluten challenge."	Clarification.
59.	Section 8.1.1.3 Rescue Medications	Added text "any exceptions to these rescue medications will require medical monitor and/or sponsor approval unless these medications are urgently required per investigator's decision. If this is urgently necessary, please notify sponsor afterwards."	Clarification.
60.	Section 8.1.3 Dose and Regimen	Updated details for use of Hemo-Nate© 18-micron blood.	Clarification.
61.	Section 8.1.3 Dose and Regimen	Removed cohort-wise and groupwise details for study subjects.	Simplification.
62.	Section 8.1.3 Dose and Regimen	Added note: Please note: TAK-101 DP is an opaque milky white suspension once reconstituted and diluted, and the placebo is a clear solution (normal saline). Both of the IV bags containing TAK-101 DP or placebo and IV tubing will be covered at the time they leave the pharmacy and remain covered throughout treatment administration.	Clarification.
63.	Section 9.1.4 Vital Sign Procedure	Added the below text: Please note the maximum body mass index (BMI) allowed is 40.	Clarification.
64.	Section 9.1.8 Procedures for Clinical Laboratory Samples	Added "wheat IgE" in the clinical laboratory tests table "Table 9.a"	Updated to further mitigate risk of potential allergic reaction in subjects with pre-existing wheat allergy
65.	Section 9.1.8 Procedures for Clinical Laboratory Samples	[redacted]	Clarification.
66.	Section 9.1.9 Contraception and Pregnancy Avoidance Procedure	Removed "effective methods of contraception" and retained only "highly effective methods of	Updated to reflect current clinical and nonclinical data.

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		contraception" at all applicable places and updated the text to reflect this, including deletion of details of "effective contraceptives" from Table 9.b.	
67.	Section 9.1.10 Pregnancy	Added minor edits and below text: The live birth should be followed up at least until 12 months post delivery.	Clarification
68.	Section 9.1.11 ECG Procedure	Added text to record 12-lead ECG in case of allergic reactions.	Clarification
69.	Section 9.1.12.1 Blood Sample (PBMC) for Tetramer Staining and ELISpot	Updated ELISpot analysis for quantifying gluten-specific T cells by removing: "If done, ELISpot analysis for T cells that produce IL-10 after ex vivo gluten peptide treatment will also be evaluated. These T cells may contribute to tolerance induction."	Clarification
70.	Section 9.1.12.2 Blood Sample (Whole Blood) for Immunophenotyping and Stimulation	Replaced description for reporting of ex vivo IL-2 assay.	Clarification.
71.	Section 9.1.12.3 Blood Cell Collection for RNA Section 9.1.12.4 Plasma Sample for Protein	Added minor edits and details for reporting and to reflect that these tests will not necessarily be done on all subjects/samples.	Clarification.
72.	Section 9.1.13.1 Collection of Plasma for PK Sampling	Added minor edits and reference to laboratory manual.	Clarification.
73.	Section 9.1.14.1 Serum Sample for Immunogenicity	[redacted]	Clarification.
74.	Section 9.1.15 Patient-Reported Outcomes Instruments	Added reference to Appendix A Table A-3.	Clarification.
75.	Section 9.1.15.1 CDSD v2.1 and Supplementary Questions (24-Hour [redacted])	Updated description for CDSD v2.1.	Clarification.
76.	Section 9.1.15.2 [redacted]	[redacted]	Simplification/clarification.

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		Recall).	
77.	Section 9.1.15.3 [redacted]	[redacted]	Clarification.
78.	Section 9.1.15.4 Additional Exploratory Questions	[redacted]	Clarification.
79.	Section 9.1.17 End of Study and End of Treatment	• Updated the EOS definition as below: End of study (EOS): This date would be the last date of study participation (ie, date of last study assessments or data collection, date of withdrawal of consent, or date of PI decision, etc.). • Updated the ET definition as below: End of treatment (ET): The date when the subject receives the last dose in the study.	Clarification.
80.	Section 9.2 Gluten Exposure Compliance	Added below text: Subjects should consume their gluten in the might of their single-day challenges and 6-day challenge.	Clarification.
81.	Section 9.2 Gluten Exposure Compliance	• Updated urine collection from "9-12 hours" to "6-12 hours" and from 24 hours for evening ingestion to 6-12 hours after gluten ingestion. • Minor edits were done.	Correction/Clarification
82.	Section 2.0 STUDY SUMMARY: Study Design: Section 6.1 Study Design Section 9.3 Schedule of Observations and Procedures Section 14.1 Study-Site Monitoring Visits	Updated COVID-19 endemic to COVID-19 pandemic.	Administrative change
83.	Section 10.1.3 Additional Points to Consider for PTEs and AEs	Added text to clarify that use of rescue medicine for "AEs related to gluten exposure" will be considered as a concomitant medication.	Clarification
84.	Section 10.1.12 Action Concerning Study Drug	• Updated the definitions for "dose not changed", "Dose Reduced", and "Drug Infusion Interrupted/Delayed." • Removed definition for "Dose Increased."	Clarification.

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		• Added definition for "Dose Rate Reduced."	
85.	Section 10.4 AESIs and Potential Risks with TAK-101 Treatment	Removed reference to clinical studies for hepatotoxicity and reference to both clinical and nonclinical data for allergy reactions, as these are discussed elsewhere in the protocol.	Clarification/simplification.
86.	Section 10.5.1 Important Identified Risks	Revised the details for adding description of IRR, adding a subheading "10.5.1.1.1 IRR Management Guidelines" and adding the reference to newly added Appendix I for management guidelines according to severity grading.	Clarification.
87.	Section 10.5.2.1 Hepatotoxicity (Reversible Liver Injury)	• Added reference to IB Edition 5 Section 6.4.2.1 for information on this potential risk. • Updated liver enzymes/bilirubin criterion for second study drug infusion on Day 8, and any subsequent dosing to "≤2 × ULN." • Added a subsection "10.5.2.1.1 Management Guidelines for Hepatotoxicity (Reversible Liver Injury)"	Clarification/Correction.
88.	Section 10.5.2.2 Thrombosis	Revised the details for description of thrombosis, by adding a subheading "10.5.2.2.1 Thrombosis management guidelines" and adding the reference to newly added Appendix J for management guidelines.	Clarification.
89.	Section 10.5.2.3 Allergic Reactions in Patients With Preexisting Wheat Allergy, Hypersensitivity, and Anaphylaxis Including WDEIA	Added details to mention that no WDEIA cases have been reported from any completed clinical study to date. Minor edits were done, and Appendix K was added for reference.	Clarification.
90.	Section 10.5.2.3.1 Management Guidelines for Allergic Reactions	Updated the subheading 10.5.2.3.1 to "Management Guidelines for Allergic Reactions" and moved the details into the newly added reference Appendix K.	Clarification.

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91.	Section 10.5.2.4 Delayed Hypersensitivity Reactions	Revised the details by adding description of delayed hypersensitivity reactions, adding a subheading "10.5.2.4.1 Management of Delayed Hypersensitivity" and adding the reference to newly added Appendix L for management guidelines.	Clarification.
92.	Section 10.5.2.4.1 Management of Delayed Hypersensitivity Appendix L Management of Delayed Hypersensitivity	Updated TAK-101 mean half-life in the details which are now moved under Appendix L.	Clarification.
93.	Section 10.5.4.1 Platelet Count Decreased	Removed the following statement: "Subjects with on-going bleeding disorders will be excluded from the studies. If a subject develops decreased platelet count after administration of TAK-101, such subjects will not receive further dosing and should be monitored/treated according to local standard of care." Minor edits were done. Created new subheading "10.5.4.1.1 Management Guidelines" with reference to Appendix M for guidelines.	Clarification.
94.	Section 2.0 STUDY SUMMARY: Efficacy Analysis: Section 13.1.3 Efficacy Analysis	Updated "Efficacy analyses of the ELISpot..." to "Efficacy analyses of the primary endpoint..." Updated "primary efficacy analysis" to "efficacy analysis of the primary endpoint."	Clarification.
95.	Section 13.1.3 Efficacy Analysis	• Updated details for primary efficacy analysis by analysis of covariance (ANCOVA). • Updated details for secondary efficacy analyses by ANCOVA and MMRM. • Added analyses for new and updated endpoints. • [redacted].	Correction and clarification of analysis plan.

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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
96.	Section 13.1.5 Biomarker Analysis	Added reference to statistical analysis plan (SAP).	Clarification.
97.	Section 13.1.6 Safety Analysis	Corrected Medical Dictionary for Regulatory Activities (MedDRA) version from 24.0 to 24.1.	Correction.
98.	Section 13.1.7 Immunogenicity Analysis	Removed details of analysis for serum ADAs.	Clarification/simplification.
99.	Section 13.1.9 Interim Analysis	Added details for an optional internal IA.	Incorporated an optional internal assessment of the impact of TAK-101 on gluten-induced symptoms and biomarkers.
100.	Section 16.0 REFERENCES	Revised as per applicable references.	Correction.
101.	Appendix A Schedule of Study Procedures Table A-1,Table A-2, Table A-3	Removed patient-reported outcomes (PROs) from Table A-1 and Table A-2 and added a separate consolidated Table A-3 with all PRO assessments.	Clarification.
102.	Appendix A Schedule of Study Procedures (Table A-1)	• Expanded the term "ET" to "Early Termination." • Updated "Day -42 to -21" to "Day -42." • Updated "Day -41 to -14" to "Day 28 ± 7." • Updated "Week -6 to -2" to "Week -4."	Clarification.
103.	Appendix A Schedule of Study Procedures (Table A-1)	• Combined concomitant medication review with PTE/AE assessment. • Added PTE/AE assessment and concomitant medication review for Visit 3.a.	Clarification.
104.	Appendix A Schedule of Study Procedures (Table **A-1**)	Removed Clinical laboratory evaluations (hematology, liver tests, and chemistry) for Visit 2, 6, 7, 8, and 9.	Optimization of blood volume for reduction of subject burden in trial scheduled activities.
105.	Appendix A Schedule of Study Procedures (Table A-1)	Revised "Additional tests: Liver, complement, tryptase, histamine, and coagulation tests only" to "Liver, complement, and coagulation tests."	Correction.

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106.	Appendix A Schedule of Study Procedures (Table A-1)	Removed urinalysis for Visit 10.a.	To reduce the subject burden in trial scheduled activities.
107.	Appendix A Schedule of Study Procedures (Table A-1)	Removed assessment of plasma sample for protein at Visits 1, 3, and 6 and for RNA at Visits 1, 3, 6, and 7.	Correction/reduction of required blood volume.
108.	Appendix A Schedule of Study Procedures (Table A-1)	Renamed [redacted] to [redacted]" and removed its assessments from Visits 3 and 7.	Correction/reduction of required blood volume.
109.	Appendix A Schedule of Study Procedures (Table A-1)	Renamed "Sampling for complement" to "Blood sampling for complement, histamine, tryptase, and CRS" and removed its assessment from Visits 5 and 9.	Correction/reduction of required blood volume.
110.	Appendix A Schedule of Study Procedures (Table A-1)	Shifted histamine and tryptase testing from Visits 3.a, 4.a, and 10.a to Visits 3, 4, and 10.	Correction.
111.	Appendix A Schedule of Study Procedures (Table A-1)	Sampling for CRS removed. Updated sample for "gliadin PK" to "PK."	Update/Clarification.
112.	Appendix A Schedule of Study Procedures (Table A-1)	Replaced footnote 'a*' with 'aψ' as below [aψ] Visits 2, 3.a, 4.a, 7, 8, 9, and 10.a can occur in the clinic or at home as deemed feasible by the sponsor/site.	Clarification.
113.	Appendix A Schedule of Study Procedures (Table A-1)	Added wheat IgE testing at screening with footnote 'p' as below: IgE should only be done (at screening) if wheat allergy is suspected and/or evaluation with allergist is required.	Clarification.
114.	Appendix A Schedule of Study Procedures (Table A-1)	Removed below text from footnote 'b' for medical history: Serologic or direct viral testing for COVID-19 may be performed according to site guidance and/or at the discretion of the investigator.	Update/clarification.
115.	Appendix A Schedule of Study Procedures	Updated footnote 'd' as below: Collect before dosing on infusion days	Clarification.

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	(Table A-1)	(Days 1 and 8, and Week 24). Hematology tests include platelet count and coagulation tests (D-dimers, PT, PTT, fibrinogen, prothrombin fragment F1+2, and thrombin-antithrombin complex). Chemistry, hematology, and liver tests can be collected if required per investigator discretion after infusion days based on if an adverse reaction occurs.	
116.	Appendix A Schedule of Study Procedures (Table A-1)	Removed below text from footnote 'e' for Liver and coagulation tests: Liver enzymes/bilirubin at Visit 3.a must be confirmed to be ≤2 × ULN before the second dose is administered at Visit 4. Added the following text: See Appendix E for details. Complement testing will be completed before and after infusion visits and 2 days (±1) after each study treatment infusion (may be performed at home or in clinic but will be analyzed by the central laboratory regardless of site of collection).	Clarification.
117.	Appendix A Schedule of Study Procedures (Table A-1)	Updated footnote 'f' for blood sampling for complement, histamine, tryptase, and CRS as below: Samples for tryptase, histamine, and complement assessment should be taken predose (within 30 minutes before dosing) and at end of infusion on each study treatment visit (Weeks 0, 1, and 24). Samples for tryptase, CRS, and histamine should be taken at middose and/or post dose, if necessary. Please see Appendix I, Appendix K, and Appendix L for further information regarding IRR and/or allergic reaction.	Reduction of required blood volume/clarification.
118.	Appendix A Schedule of Study Procedures (Table A-1)	Added below text to footnote 'j' for gluten challenge: Refer to Table A-3 for full details on PRO assessments.	Clarification.

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	Location	***Description***	***Rationale***
119.	Appendix A Schedule of Study Procedures (Table A-1)	Updated footnote 'm' for plasma sample for protein and blood sample for RNA as below: Plasma sample for protein will be collected before and 4 hours after each gluten challenge at run-in and at Weeks 2, 8, 14, and 20. Blood sample for RNA will be collected before and 4 hours after each gluten challenge at run-in and at Weeks 2, 14, and 20.	Clarification/reduction of required blood volume.
120.	Appendix A Schedule of Study Procedures (Table A-1	[redacted]	Clarification/correction.
121.	Appendix A Schedule of Study Procedures (Table A-1)	Added new footnote 'o' for telephone follow-up visit with below text: "Subjects who complete an ET visit do not require a telephone follow up."	Correction.
122.	Appendix A Schedule of Study Procedures (Table A-1)	Added new footnote 'q' with below text: "Plasma sample for PK will be taken predose, mid-dose, and after dose for Visit 3. For Visits 4 and 10, these PK samples will be taken at middose and after dose."	Correction
123.	Appendix A Schedule of Study Procedures (Table A-1)	Added new footnote 'r' for urine sample for gluten to add reference to Table A-2.	Clarification.
124.	Appendix A Schedule of Study Procedures (Table A-2)	Updated the table header to remove "at home."	Clarification.
125.	Appendix A Schedule of Study Procedures (Table A-2)	Added 'Gluten challenge daily diary' for Day 15.	Clarification.
126.	Appendix A Schedule of Study Procedures (Table A-2)	Added a row for blood sample for biomarkers on Visit 5 and Visit 6 with new footnote 'b' with text as below: Blood sample will be taken in the clinic.	Clarification.

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127.	Appendix A Schedule of Study Procedures (Table A-2)	Added following text to footnote 'a' for site of gluten challenge and gluten challenge daily diary: If necessary, for Days 16-19, the gluten challenge can also be done in clinic with sponsor approval.	Clarification.
128.	Appendix A Schedule of Study Procedures (Table A-2)	Updated footnote 'c' for 'Urine sample for gluten' to replace 'predose' with 'pre–gluten challenge.'	Clarification.
129.	Appendix A Schedule of Study Procedures (Table A-3)	Added separate table for Schedule of Study Procedures for PROs.	Clarification.
130.	Appendix E	Updated liver enzymes criterion for second study drug infusion post first infusion to "≤2 × ULN."	Correction
131.	Appendix I	Added new appendix: IRR Management Guidelines.	Update to clarify and improve assessment and management of potential infusion-related reactions.
132.	Appendix J	Added new appendix: Thrombosis Management Guidelines.	Update to clarify and improve assessment and management of potential thrombosis.
133.	Appendix K	Added new appendix: Management Guidelines for Allergic Reactions.	Update to clarify and improve assessment and management of potential allergic reactions.
134.	Appendix L	Added new appendix: Management of Delayed Hypersensitivity.	Update to clarify and improve assessment and management of potential delayed hypersensitivity reactions.
135.	Appendix M	Added new appendix: Management of Platelet Count Decreased.	Update to clarify and improve assessment and management of potential platelet count decreased.
136.	Appendix O	Replaced CoFAR Specific Grading System for Severity of Allergic Reactions and Treatment	Update to clarify and improve assessment and management of potential allergic reactions.

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		with Severity Grading System for Acute Allergic Reactions in Adults (AAR Grading) in all applicable places in the protocol.	
137.	Appendix P	Updated appendix heading: Management Guidelines for Acute Allergic Reactions in Adults if CoFAR Grade 3 and Above Reactions Occur Following the Administration of TAK-101.	Update to clarify and improve assessment and management of potential acute allergic reactions in adults.
138.	Appendix Q	Added new appendix: Clinical Subgrading for Assessment of Severity of Acute Allergic Reactions (AAR) in Adults.	Update to clarify and improve assessment and management of potential allergic reactions.
139.	Appendix R	Added new appendix: Identification, Monitoring, and Treatment of Delayed Hypersensitivity Reactions.	Update to clarify and improve assessment and management of potential allergic reactions.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-101	
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	**IND No.:** 017579	**EU CT No.:** Not Applicable
Study Number: TAK-101-2001	**Phase:** 2	

Study Design:

This is an adaptive 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). The study comprises 2 cohorts (Cohort 1 and Cohort 2). Cohort 2 may include 1 or 2 additional dose levels, depending on safety, tolerability, and activity observed in Cohort 1. Approximately 90 adult subjects (18 per arm) between the ages of 18-75 years with well-controlled biopsy-confirmed CeD on a GFD for at least 6 months are planned to be enrolled. Subjects will receive a total of 3 doses of TAK-101 and/or placebo. Randomized subjects will receive 2 intravenous (IV) infusions of TAK-101 and/or placebo on Days 1 and 8, and a third dose of TAK-101 IV infusion will be administered at Week 24.

First cohort at the TAK-101 25 µg/kg Gluten Epitopes (GE) (2 mg/kg PLGA NP) dose level:

Approximately 45 subjects will be randomly assigned into 1 of 3 treatment groups with a 1:2:2 randomization ratio in the first study cohort:

- Group A: Two infusion doses of placebo, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.
- Group B: One infusion dose of 25 µg/kg GE TAK-101 on Day 1 followed by 1 infusion dose of placebo on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.
- Group C: Two infusion doses of 25 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.

If it is deemed appropriate to enroll both the TAK-101 50 µg/kg GE (4 mg/kg PLGA NP) and the 12.5 µg/kg GE (1 mg/kg PLGA NP) dose levels in Cohort 2, Cohort 2 will consist of 45 subjects randomly assigned to 1 of 3 treatment groups with a 1:2:2 randomization ratio:

- Group A: Two infusion doses of placebo, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.
- Group D: Two infusion doses of 50 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 50 µg/kg GE TAK-101 at Week 24.
- Group F: Two infusion doses of 12.5 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 12.5 µg/kg GE TAK-101 at Week 24.

If it is decided to include 12.5 µg/kg GE (1 mg/kg PLGA NP) but not the 50 µg/kg GE (4 mg/kg PLGA NP) dose level in Cohort 2, Cohort 2 will consist of 27 subjects randomly assigned to 1 of 2 treatment groups with a 1:2 randomization ratio:

- Group E: Two infusion doses of placebo, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 12.5 µg/kg GE TAK-101 at Week 24.
- Group F: Two infusion doses of 12.5 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 12.5 µg/kg GE TAK-101 at Week 24.

If neither 50 µg/kg GE nor 12.5 µg/kg GE is recommended to be tested, the study will terminate enrollment.

In addition, the IDMC will review safety and laboratory data from the third infusions given to the first 5 subjects and, if needed, the IDMC will make recommendations as appropriate.

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Subjects aged 18 to 75 years, inclusive, with documented history of well-controlled biopsy-confirmed CeD, and on a GFD for a minimum of 6 months, will be screened for enrollment. 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 confirm 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), and 1 IV infusion dose of TAK-101 at Week 24. Subjects will be randomly assigned to receive placebo and/or TAK-101 at doses of 25 µg/kg GE in the first study cohort. In the second study cohort, subjects will be randomly assigned to receive placebo and/or TAK-101 at doses of either 50 µg/kg GE or 12.5 µg/kg GE. For both study cohorts, the maximum dose of TAK-101 to be administered will be 6250 µg GE per dose. Randomization will be stratified based on HLA Class II:

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

HLA distribution will be monitored throughout the study and enrollment of subjects in certain strata may be limited in order to reflect the known distribution of HLA types in the CeD population.

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 3 single-day 3 g gluten challenges at Weeks 8, 14, and 20. With the exception of these series of gluten challenges, subjects will be required to continue to follow a GFD throughout the duration of the study.

For the third dose, all randomized subjects will receive the same dose of TAK-101 that they received with initial treatment, and all subjects initially randomized to placebo will receive 25 µg/kg GE TAK-101 or 12.5 µg/kg GE TAK-101, if it is decided not to include the 50 µg/kg GE dose level in Cohort 2.

Subjects will be observed for treatment-emergent adverse events (TEAEs), including infusion-related reactions (IRRs), potential allergic reactions, and drug-induced cytokine release syndrome (CRS), for 2 hours following each study drug infusion. Subjects will be assessed regularly for safety and tolerability by TEAEs, physical examination, vital signs, and routine clinical laboratory tests (chemistry, liver tests, and hematology).

Samples will be collected for safety-related endpoints and monitoring for AESIs. To understand drug activity, samples will be taken to measure the number of gliadin-specific T cells; changes in blood cell immunophenotyping for gut-homing CD4, CD8, and γδ cells; IL2 levels; and PK assessments 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 out of window visits and/or 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 the last subject has completed all procedures and assessments or discontinued the study early. After final database lock, the study will be unblinded and a clinical study report will be prepared.

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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 HLA-DQ2.5 positive subjects treated with TAK-101 versus placebo.

Secondary Objectives:

- Evaluate the safety and tolerability of TAK-101.
- Evaluate gluten-induced CeD symptoms in subjects treated with TAK-101 versus placebo.
- Characterize the durability of immune tolerance mediated by TAK-101 based on gluten challenge induced plasma interleukin (IL)-2.
- Measure plasma concentration of TAK-101.
- Assess the immunogenicity of various dose levels and dose regimens of TAK-101.

Subject Population: Subjects aged 18 to 75 years, inclusive, who are HLA-DQ2.5 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 90 subjects randomized Cohort 1 (n=45); Cohort 2 (if both dose levels, n=45, or if only one dose level, n=27).	Estimated total: Approximately 58 sites globally.
Dose Level(s): Cohort 1: Group A = Placebo: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 25 µg/kg GE at Week 24 Group B = TAK-101 25 µg/kg GE: 1 infusion dose; placebo: 1 infusion dose, 1 week apart; followed by 1 infusion dose of 25 µg/kg GE at Week 24 Group C = TAK-101 25 µg/kg GE: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 25 µg/kg GE at Week 24 Cohort 2 (if Cohort 1 safety data review supports both 50 µg/kg GE and 12.5 µg/kg GE): Group A = Placebo: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 25 µg/kg GE at Week 24 Group D = TAK-101 50 µg/kg GE: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 50 µg/kg GE at Week 24 Group F = TAK-101 12.5 µg/kg GE: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 12.5 µg/kg GE at Week 24 Cohort 2 (if Cohort 1 safety data review supports only 12.5 µg/kg GE) Group E = Placebo: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 12.5 µg/kg GE at Week 24 Group F = TAK-101 12.5 µg/kg GE: 2 infusion doses, 1 week apart; followed by 1 infusion dose of 12.5 µg/kg GE at Week 24	**Route of Administration:** IV infusion over approximately 2 hours.

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Duration of Treatment:	**Period of Evaluation:**
24 weeks (initial treatment to final gluten challenge, with third dose of TAK-101 at Week 24).	Up to 24 weeks of treatment, up to 6 weeks of screening, and 1 month of follow-up post treatment.

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 to the best of their capability for ≥6 months.
- HLA-DQ2.5 and/or HLA-DQ8 positive during screening laboratory testing.

Main Criteria for Exclusion:

- The presence of other inflammatory GI disorders or systemic autoimmune diseases that either have the potential to cause persistent GI symptoms similar to celiac disease or are not well controlled without the use of excluded medications.
  - Examples of conditions that are exclusionary include: inflammatory bowel disease, eosinophilic gastroenteritis or colitis, and microscopic colitis requiring treatment in the 6 months before screening.
  - Examples of conditions that may be permissible after discussion with the medical monitor/or sponsor include: systemic autoimmune disease such as scleroderma, psoriatic or rheumatoid arthritis, lupus that is stable and without GI involvement, well-controlled autoimmune thyroid disease, well controlled type 1 diabetes or proton pump-inhibitor responsive eosinophilic esophagitis in symptomatic and histologically confirmed remission.
- Has known or suspected refractory CeD or ulcerative jejunitis.
- Has known or suspected allergy to wheat, such as hypersensitivity and/or anaphylaxis including wheat-dependent-exercise induced anaphylaxis (WDEIA). If there is a possible history of urticaria, angioedema, or anaphylaxis to wheat, investigators should perform testing for wheat anti-immunoglobulin E (IgE) antibodies or refer to an allergist for evaluation prior to enrollment to rule out any of these allergies.
- 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.
- Has known or suspected clinically significant liver disease or positive test result 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).
- Has baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5× the ULN, or total bilirubin >1.5× the ULN unless subject has known Gilbert's syndrome that can explain the elevation of bilirubin.
- Has an ongoing infection such as COVID-19 at the time of screening (additional testing may be performed at the discretion of the investigator).
- History of previous thromboembolic events or active bleeding disorders.
- Has known allergy to or intolerance of TAK-101 or any of its ingredients or excipients.

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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 in HLA-DQ2.5-positive subjects based on results of a gliadin-specific enzyme-linked immunospot (ELISpot) assay.

Secondary Endpoints:

- Safety and tolerability as assessed by TEAEs, AESIs, physical examinations, vital signs, and clinical laboratory testing, including liver tests.
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day average nausea severity score measured in Celiac Disease Symptom Diary version 2.1 (CDSD v2.1, 24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly GI symptom severity score (CDSD v2.1, 24-Hour Recall).
- Comparison between the pre/post gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20.
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at each of the following time points: run-in (Visit 2), Day 15, and Weeks 8, 14, and 20.
- Plasma concentration of TAK-101 on dosing days.
- Serum concentration of ADAs to various doses of TAK-101 (DGP-IgG).

Note: Changes in run-in (Visit 2) and Week 8, 14, and 20 will be calculated using the difference of average scores.

Statistical Considerations:

Analysis Sets:

The Randomized Analysis Set will consist of all subjects who were randomized. Subjects will be analyzed according to the treatment they were randomized to.

The full analysis set (FAS) will consist of all randomized subjects who received 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 HLA-DQ2.5-positive 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 measurable PK concentration.

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.

Efficacy Analysis:

Efficacy analyses of the primary endpoint will be analyzed using the biomarker analysis set. All other efficacy analyses will be based on the FAS unless stated otherwise. 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 dose 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 arm. 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 TAK-101 dose arm with

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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.

- TAK-101 50 µg/kg GE 2 infusions versus placebo.
- TAK-101 25 µg/kg GE 2 infusions versus placebo.
- TAK-101 25 µg/kg GE 1 infusion versus placebo.
- TAK-101 12.5 µg/kg GE 2 infusions 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 postbaseline time point will be analyzed using an ANCOVA model.

- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day average nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly GI symptom severity score in CDSD v2.1 (24-Hour Recall).
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20.
- The continuous longitudinal endpoints will be analyzed by mixed model for repeated measures (MMRM) approach. The model will include fixed effects for the treatment group, visit, treatment-by-visit interaction, and 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. If the model does not converge, additional covariance structure will be used in the order specified in the statistical analysis plan. 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.
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the- pre to post–gluten challenge change in 3-day average nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly GI symptom severity score in CDSD v2.1 (24-Hour Recall).
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20.
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at each of the following time points: run-in (Visit 2), Day 15, and Weeks 8, 14, and 20.

Safety Analysis:

Safety analyses will be performed using the safety analysis set. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 24.1 or later). Data will be summarized using preferred terms 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.

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Interim Analysis

A safety interim analysis (IA) is planned when 30 subjects reach the primary endpoint on Day 20 of Cohort 1. After a review of Cohort 1 data, a decision will be made either to stop the study or continue the study by dosing the second study cohort (ie, Cohort 2). This decision will be made by the sponsor study team, based on the recommendations of the study's IDMC.

In addition to the IA for the IDMC to review, an optional internal IA will be conducted by an internal unblinded team, after the IDMC IA when all of Cohort 1 subjects have completed Visit 7 or early terminated, to assess potential effects of TAK-101 on gluten-induced symptoms and immune biomarkers. The optional internal IA may include exploratory evaluation of PK and ADA.

Sample Size Justification: The planned sample size is approximately 90 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 50 µg/kg GE), a sample size of 90 subjects (18 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. Assuming 17% of the subjects will drop out or are not HLA-DQ2.5 positive, approximately 90 subjects will be randomized (18 subjects per arm).

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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

The sponsor 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.

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3.3 List of Abbreviations

γδ	gamma delta
AAR	acute allergic reaction
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
APC	antigen presenting cells
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
CTCAE	Common Terminology Criteria for Adverse Events
DGP	deamidated gliadin peptide
DP	drug product
DTH	delayed type hypersensitivity
ECG	electrocardiogram
eCRF	electronic case report form
ELISpot	enzyme-linked immunospot
EOS	End of study
ET	End of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GE	gluten epitopes
GFD	gluten-free diet
GI	gastrointestinal
GLP	Good Laboratory Practice
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
IB	Investigator Brochure

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ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	independent data monitoring committee
IFN-γ	interferon-gamma
IgA	immunoglobulin A
IgG	immunoglobulin G
IgE	immunoglobulin E
IL	interleukin
INR	international normalized ratio
IP	investigational medicinal product
IRR	infusion-related reaction
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LFT	liver function test
MARCO	macrophage receptor with collagenous structure
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MMRM	mixed model for repeated measures
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
NP	nanoparticle
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
PK	pharmacokinetic(s)
PLGA	poly (lactic-co-glycolic acid)
PLGA-Ag	poly (lactic-co-glycolic acid)-antigen
PPI	proton pump inhibitor
PPS	per protocol set
PRO	patient-reported outcome
PTE	pretreatment event
SAE	serious adverse event
SFU	spot forming units
SUSAR	suspected unexpected serious adverse reaction
TEAEs	treatment-emergent adverse events
Th1	Type 1 Helper T cells
tTG	tissue transglutaminase
UK	United Kingdom

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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

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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 (Ludvigsson et al. 2013). 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 (Shan et al. 2002). 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-DQ2.5/-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 (Han et al. 2013). The tissue proinflammatory response includes interferon-gamma (IFN-γ) release along with the release of metalloproteinases and other tissue damaging mediators (Mohamed et al. 2006; Nilsen et al. 1998). Intestinal injury is characterized by villous atrophy, crypt hyperplasia, and infiltration of lymphocytes in both the epithelium and lamina propria. Antibody-mediated inflammation, such as immunoglobulin A (IgA) anti-transglutaminase 2 autoantibodies, is thought to drive extraintestinal manifestations, such as dermatitis herpetiformis (Leffler 2011). 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%) (Leonard et al. 2017) and approximately 0.5% globally (Lionetti et al. 2015).

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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 (Catassi et al. 2007; Gibert et al. 2013). 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 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 (Garber et al. 2017; Leffler et al. 2013). The reasons for this heterogeneity in gluten sensitivity is unclear but may be related to both genetic predisposition and microbiome influences (Caminero et al. 2019; Vader et al. 2003). 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 (Lebwohl et al. 2013; Lebwohl et al. 2014).

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 (Hall et al. 2013). 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 (Comino et al. 2016; Costa et al. 2019; Moreno et al. 2017). 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 (Syage et al. 2018). 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 (Lerner et al. 2019). Finally, a study from Canada directly measured gluten in reserved portions of meals (ie, doggie bags) that patients with CeD saved from each meal. The reserved portions of meals were tested by a certified laboratory and found that 86% of patients with CeD were exposed to gluten over a 10-day period (Silvester et al. 2019).

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4.1.2 Name and Description of Study Drug

TAK-101 drug substance is immunogenic CeD-related gluten epitopes in gliadin-enriched wheat-based extract. The manufacturing process results in an extract that reduces the amount of high molecular weight (HMW) polymers and enriches the water-alcohol soluble gliadin/glutenin monomers. Gliadin proteins comprise approximately 50% of wheat total proteins and are the major antigenic factors in CeD (Schopf et al. 2021).

TAK-101 drug product (DP) is composed of 12.5 µg of immunogenic GE incorporated per mg of poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs). TAK-101 NPs are negatively charged with an average size between 400 and 800 nm. TAK-101 NPs are intended to induce tolerogenic immune response to gluten in subjects with CeD.

TAK-101 DP is supplied as a lyophilized powder containing 12.5 µg GE per mg of PLGA NPs, with each vial containing nominally 1250 µg GE (100 mg PLGA NP) with cryoprotectant excipients (sucrose and mannitol). TAK-101 DP is filled into Type 1 glass vials, lyophilized, and sealed with rubber stoppers and aluminum seal with plastic flip-off caps. The lyophilized powder is reconstituted in sterile water for injection. The reconstituted TAK-101 is further diluted in 0.9% sodium chloride intravenous infusion bag and filtered through a disposable 18 µm stainless steel filter, prior to intravenous administration using a controlled infusion device (ie, infusion pump). Vials are packaged in boxes and are designated for single use.

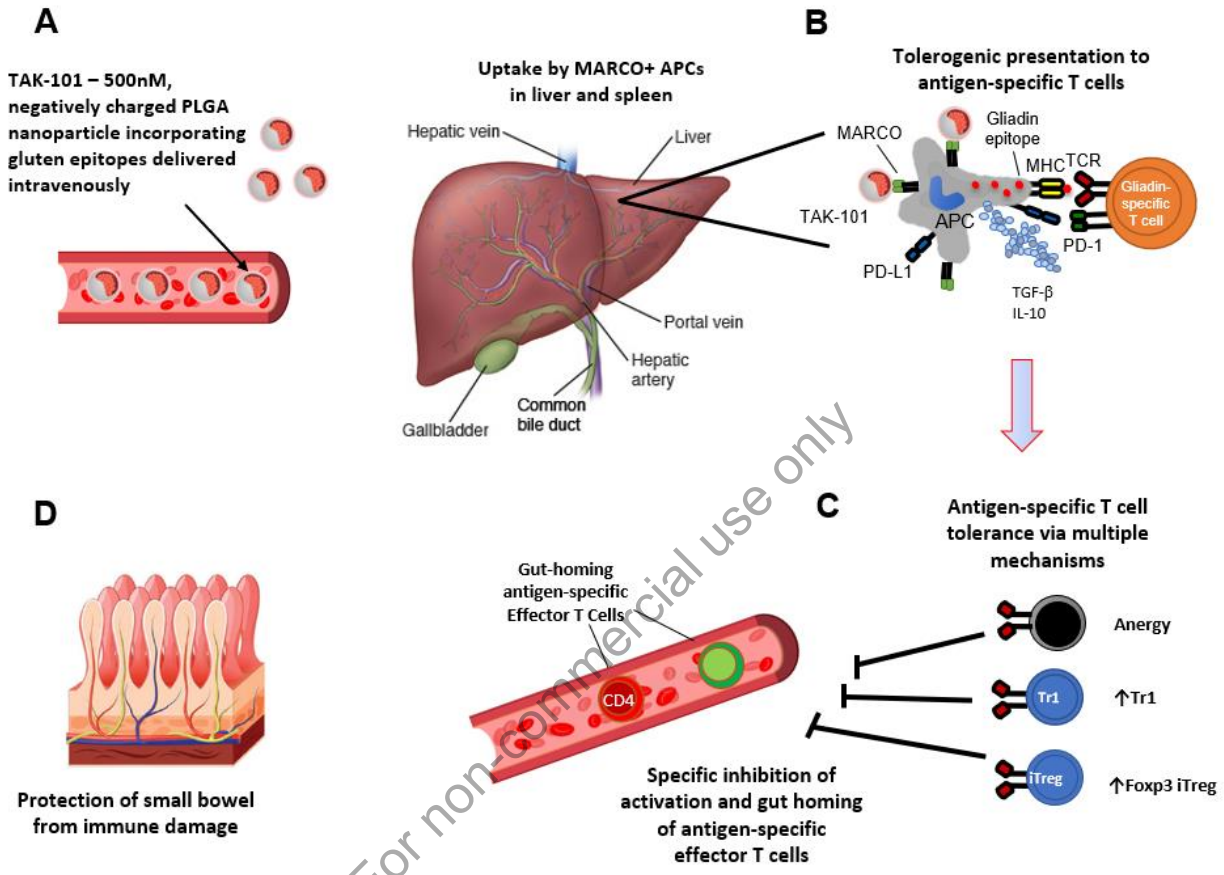
In a prior phase 2a study (Study TGLIA-5.002), efficacy and pharmacodynamics (PD) data suggested that TAK-101 can reduce or prevent immune activation and intestinal damage

triggered by gluten exposure in patients with CeD. On the basis of these data, TAK-101 is expected to improve symptoms and reduce small intestinal mucosal injury in patients with inadequate response to dietary modification (Kelly et al. 2021).

The proposed mechanism of action of TAK-101 is as follows: TAK-101 NPs are designed within a set of parameters that are intended to minimize the risk of an unwanted immune response to the incorporated gluten or toxicity due to the NPs and promote the induction of immune tolerance to gluten (gliadin) through uptake and processing by antigen presenting cells (APCs) in the spleen and liver. APCs process the gluten antigens into epitopes that bind to HLA Class II T cells, with the appropriate T cell receptor, interact with the APC via peptide bound HLA Class II in such a way that T cell tolerance rather than activation is induced. Immune tolerance is thought to be the result of gluten-specific T cell deletion, anergy, and/or induction of regulatory T cells. PLGA-antigen (PLGA-Ag) NPs are believed to target APCs responsible for scavenger receptor-dependent uptake and disposal of a wide variety of antigens, while maintaining self tolerance (Getts et al. 2011). Thus, we propose that carboxylated PLGA-Ag NPs are treated in a similar fashion as apoptotic debris, triggering synergistic tolerance mechanisms that evolved to deal with disposal after normal apoptotic cell death, while avoiding immune activation (Kelly et al. 2021).

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Figure 4.a TAK-101: Mechanism of Action



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Source: Adapted from (Kelly et al. 2021)

APCs: antigen-presenting cells; Foxp3iTreg: Forkhead box-p3 as induced regulatory T cell; IL-10: interleukin-10; iTreg: induced regulatory T cell; MARCO: macrophage receptor with collagenous structure; MHC: major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PLGA: poly (lactic-co-glycolic acid); TCR: T cell receptor; TGF-β: transforming growth factor beta; Tr1: type 1 regulatory T cells.

Antigen refers to celiac-related gluten epitopes from enriched-gliadin extract.

The potential for TAK-101 to render gliadin-reactive T cells tolerant to gluten could potentially abrogate or reverse the underlying pathology of CeD and reduce symptoms and intestinal damage related to ongoing active disease, reduce the burden associated with a lifetime adherence to a GFD, and lower the risk of serious comorbidities associated with CeD such as cancer.

The TAK-101 mechanism of action reduces immune reactions to specific proteins. When applied to autoimmune diseases like CeD, TAK-101 allows for targeted and durable reduction of unwanted gliadin-reactive T cell responses, while leaving the remainder of the immune system intact (Kelly et al. 2021).

4.1.3 Purpose for New TAK-101 Dosage Nomenclature

The sponsor updated the dosage nomenclature in concordance with the current manufacturing process and release specifications and to align globally across countries, by reporting the quantity of GEs measured in the NP (µg of GE), rather than the units of PLGA polymer of the NP, as previously reported (mg PLGA). The sponsor has implemented this change throughout all study-related documents. This change does not result in a change in the actual amount of PLGA or gliadin-derived protein administered to subjects at a given dose level but allows clarity regarding the quantity of immunogenic peptides administered. Nomenclature details are summarized in Table 4.a. **Note:** For every 1 mg/kg of PLGA NP, the dose will be 12.5 µg/kg GE.

Table 4.a TAK-101 New Dosage Nomenclature

Prior Nomenclature (mg PLGA NP Per Kg Subject Weight)	New Nomenclature (µg of GE Per Kg Subject Weight)
1 mg/kg	12.5 µg/kg
2 mg/kg	25 µg/kg
4 mg/kg	50 µg/kg
8 mg/kg	100 µg/kg
Max dose: 500 mg	**Max dose: 6250 µg**

GE: gluten epitope; Max: maximum; NP: nanoparticle; PLGA: poly (lactic-co-glycolic acid).

The vials are supplied in 1250 µg GE (100 mg PLGA NP). Please refer to the TAK-101-2001 Pharmacy Manual for any additional information regarding the investigational product.

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4.1.4 Summary of Nonclinical Findings

After IV injection, TAK-101 interacts with APCs via the scavenger receptors such as macrophage receptor with collagenous structure (MARCO) (Getts et al. 2015). The APCs then present gliadin peptides, in the context of major histocompatibility complex (MHC) Class II (MHC is analogous to HLA in humans), to CD4 T cells in the spleen and liver. Antigen presentation under these conditions in mice results in tolerance. An IV infusion of TAK-101 reduced gliadin-specific immune responses in multiple mouse models, including reductions in gliadin-specific antibodies and reductions in inflammatory cytokines produced by gliadin-specific T cells. These studies suggest that tolerance is the result of early anergy and regulatory T cell induction (Freitag et al. 2020). Taken collectively, the in vivo pharmacology data support the activity of TAK-101 in physiologic systems involved in CeD at the proposed human doses.

4.1.4.1 Nonclinical Safety Summary

In relevant single- and repeat-dose general toxicity studies up to 3 months, the major findings identified in rats and monkeys were liver toxicity, increases in circulating complement components, and/or decreases in platelets. Additional rat-specific findings consisted of increased

histiocytic cellularity of the splenic red pulp and sporadic cellular infiltrates in the lungs. All findings demonstrated evidence of reversibility. The no-observed-adverse-effect level (NOAEL) from 3-month toxicity studies in rats, the most sensitive species, was 937.5 µg/kg GE (HED of approximately 150 µg/kg GE) and in monkeys was 937.5 µg/kg GE (HED approximately 300 µg/kg GE).

There were no safety pharmacology toxicities of concern identified on a panel of in vitro assays recommended by the National Cancer Institute (NCI) Nanotechnology Characterization Laboratory (NCL), which was designed specifically for the evaluation of NPs being developed for clinical use (ncl.cancer.gov/resources/assay-cascade-protocols), or on in vitro hepatotoxicity or immunotoxicity safety pharmacology assays. There were no reproductive or developmental toxicities of concern at maternally tolerated dose levels in GLP embryofetal development or fertility and early embryonic development studies in rats.

A 2-dose bridging study was conducted to demonstrate the comparability of the toxicity profiles between TAK-101 DP manufactured by Process A and Process B. The observed toxicities were similar between TAK-101 manufactured by either process and consistent with findings observed in general toxicity studies.

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The reproductive and developmental toxicity of TAK-101 was evaluated in preliminary embryo-fetal development studies conducted in rats and rabbits, and a definitive embryo-fetal development study in rats. In the definitive embryo-fetal developmental study in rats, no TAK-101–related effects on intrauterine growth and survival or fetal morphology (external, visceral, and skeletal) were observed. The NOAEL for maternal toxicity was considered to be 625 µg/kg GE, and the NOAEL for embryo-fetal development was 1250 µg/kg GE. In the preliminary embryo-fetal development study in rabbits, no TAK-101-related effects on intrauterine growth and survival or fetal morphology (external and visceral) were observed at the highest tolerated dose of 625 µg/kg GE. At nontolerated dose levels, higher mean litter proportions of postimplantation loss and correspondingly lower mean numbers of live fetuses were noted and were considered secondary to maternal toxicity with decreased food consumption and weight loss.

4.1.5 Summary of Clinical Findings

Phase 1 Study (Study # TGLIA-5.001)

The phase 1 program was designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending IV doses of TAK-101 in subjects aged 18 to 75 years with biopsy-confirmed CeD. Study 5.001 included 2 parts: single ascending doses (SAD) which ranged from 1.25 to 100 µg/kg GE of TAK-101 (Part A), and repeated doses of TAK-101 of 25, 50, 100 µg/kg GE of TAK-101 on Days 1 and 8 (Part B). This study was conducted in otherwise healthy subjects with well-controlled CeD 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 1.25 and 6.25 µg/kg GE; 3 subjects each received doses of 12.5, 25, and 50 µg/kg GE; and 4 subjects received 100 µg/kg GE. Fourteen of 17 subjects reported at least 1 AE. Most of the AEs reported were mild to moderate in severity. There were no deaths or SAEs reported in this study, and 1 subject withdrew from the study due to an IRR TEAE attributed to the study drug. Additional data including independent data monitoring committee (IDMC) recommendations regarding IRRs and TEAE tables can be found in the Investigator Brochure (IB) Edition 5.

In Part B of the study, a total of 6 subjects were enrolled sequentially. Two subjects received 2 doses of 25 µg/kg GE, 2 subjects received 2 doses of 50 µg/kg GE, and 2 subjects received 2 doses of 100 µg/kg GE. Five of 6 subjects reported at least 1 TEAE. All the reported TEAEs were mild in severity except for 1 case of Grade 2 headache. There were no deaths or SAEs reported in this study, and no subjects withdrew from the study due to an AE attributed to the study drug administration. Additional data and TEAE tables can be found in the IB Edition 5.

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Phase 2a Study (Study # TGLIA-5.002)

The completed phase 2a Study TGLIA-5.002 investigated the safety, efficacy, PD, and PK in subjects with well-controlled CeD after an oral gluten challenge who were administered 100 µg/kg GE per infusion up to a maximum dose of 8125 µg GE per infusion of TAK-101 or placebo on Days 1 and 8. 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 treated versus placebo-treated subjects. A total of 34 subjects were treated in the study; with 16 subjects in TAK-101 and 18 in placebo groups respectively. 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% (Kelly et al. 2021).

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 and epithelial-interacting T cells (a4b7+ and/or aEb7+) in the TAK-101 treated group compared to controls suggesting reduction of gut localized effector cells in the setting of gluten exposure.

The modified infusion volume, duration, and rate implemented in the phase 1 study Part B was employed in this phase 2a study.

TEAEs were reported for all 34 subjects (100%) who received the study drug in the Study TGLIA-5.002. There were no deaths or SAEs reported in this study, and no subjects withdrew from the study due to an AE attributed to the study drug administration. All 16 subjects in the treatment arm reported at least 1 or more TEAEs; all 18 subjects in the placebo arm reported 1 or more TEAEs. Most of the TEAEs reported were mild to moderate in severity. Additional data and TEAE tables can be found in the IB Edition 5.

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 100 µg/kg GE 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, TEAEs were of mild intensity, and no SAEs were reported.

The totality of data supports further development of TAK-101. In vitro and nonclinical data have shown hepatotoxicity with a relatively low safety margin compared with the 100 µg/kg GE dose and support the use of TAK-101 at a lower dose. Nonclinical pharmacology studies suggest doses lower than 100 µg/kg GE could also be efficacious.

The current study has been designed to assess lower dose levels and single-dose regimens that may be active as predicted by nonclinical modeling, to assess durability of treatment effect, and to confirm the safety and activity seen in the prior phase 2a study.

The key endpoint used to explore the dose response relationship will be gluten-specific T cell response to gluten challenge in HLA-DQ2.5–positive subjects (based on IFN-γ ELISpot) as used in the prior phase 2a study. This analysis may provide evidence supportive of single dose induction, thereby further reducing the risk of IRR and patient burden. Additional data may include gluten-specific T cells as measured with HLA-DQ2.5 tetramers, interleukin (IL)-2 response and durability of protection from symptoms and IL-2 release with gluten exposure up to 20 weeks post treatment. Data collected 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, the management for patients with CeD is a GFD, which involves strict, lifelong avoidance of gluten exposure. The GFD is not considered 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. Efficacy/pharmacodynamic data from the phase 2a study suggests that TAK-101 can reduce or prevent immune activation and intestinal damage triggered by gluten exposure in patients with CeD. Given this data, TAK-101 is expected to improve symptoms and reduce small intestinal mucosal injury in patients with inadequate response to dietary modification.

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Phase 1 and 2a studies of TAK-101 have demonstrated an acceptable safety and tolerability profile. Phase 2a data demonstrated 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. The TEAEs reported were mild to moderate in severity. No SAEs have been observed in the clinical studies and only one subject was discontinued due to an IRR in a phase 1 study (Kelly et al. 2021).

IRR is an important identified risk with the administration of TAK-101. Important potential risks with the administration of TAK-101 are hepatotoxicity (reversible liver injury) based on nonclinical data, thrombosis based on nonclinical data, and theoretical risk of allergic reactions in subjects with preexisting wheat allergy, hypersensitivity, and/or anaphylaxis including wheat-dependent-exercise induced anaphylaxis (WDEIA). Additionally, there is a potential risk of platelet count decreased. All these risks are designated as adverse events of special interest (AESI) that will be further characterized during future clinical development programs of TAK-101, however only IRRs have been observed in clinical trials to date. There are risk mitigation measures in place for these risks. Overall, the benefit risk profile supports continuing clinical development of TAK-101.

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4.3.1 Risk Related to Oral Gluten Exposure

Potential risks of gluten exposure include development of signs and/or symptoms of CeD, including GI symptoms (such as abdominal pain, bloating and diarrhea) and extraintestinal manifestations (such as skin rash), neurological/neurocognitive manifestations (such as brain fog), elevation in liver aminotransferases and bilirubin, and/or joint pain. Gluten challenge has been used clinically and in research for decades. Most CeD studies have used longer duration and/or higher dose gluten in their gluten challenges than what is planned in the current study. Any signs/symptoms of study-related gluten exposure are expected to resolve within 48-72 hours after gluten exposure is ceased. The gluten challenge is not expected to result in any increase in risk of future CeD complications.

It is known that response to gluten exposure is very heterogeneous with some patients having minimal response and some having a severe response. In this study, the run-in gluten challenge (3 g of gluten), administered before treatment with TAK-101 or placebo, allows subjects to serve as their own controls so that gluten responses through the study can be compared within subjects to understand the change in response before and after treatment with TAK-101. In addition, the run-in gluten challenge allows subjects to understand better their own gluten reaction and confirm willingness to continue in the study before receiving study treatment. Finally, the potential risk of allergic reactions to wheat is being mitigated by excluding patients with known hypersensitivity or allergy to wheat from the study and by monitoring for any IRRs during and after the infusion.

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 HLA-DQ2.5 positive subjects treated with TAK-101 versus placebo.

5.1.2 Secondary Objectives

Secondary objectives of this study are to:

- Evaluate the safety and tolerability of TAK-101.
- Evaluate gluten-induced CeD symptoms in subjects treated with TAK-101 versus placebo.
- Characterize the durability of immune tolerance mediated by TAK-101 based on gluten challenge–induced plasma IL-2.
- Measure plasma concentration of TAK-101.
- Assess the immunogenicity of various dose levels and dose regimens of TAK-101.

5.1.3 Exploratory Objectives

[redacted]

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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 in HLA-DQ2.5–positive subjects based on results of a gliadin-specific ELISpot assay.

5.2.2 Secondary Endpoints

Secondary endpoints of this study are:

- Safety and tolerability as assessed by TEAEs, AESIs, physical examinations, vital signs, and clinical laboratory testing, including liver tests.
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day average nausea severity score measured in Celiac Disease Symptom Diary version 2.1 (CDSD v2.1, 24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly GI symptom severity score (CDSD v2.1, 24-Hour Recall).
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20.
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at each of the following time points: run-in (Visit 2), Day 15, and Weeks 8, 14, and 20.
- Plasma concentration of TAK-101 on dosing days.
- Serum concentration of ADAs to various doses of TAK-101 (deamidated gliadin peptide [DGP]- immunoglobulin G [IgG]).

Note: Changes in run-in (Visit 2) and Weeks 8, 14, and 20 will be calculated using the difference of average scores.

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5.2.3 Exploratory Endpoints

[redacted]

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is an adaptive 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. The study comprises 2 cohorts (Cohort 1 and Cohort 2). Cohort 1 will investigate 1 active dose level. Cohort 2 may include 1 or 2 additional active dose levels, depending on safety, tolerability, and activity observed in Cohort 1. This study is adaptive, and dosing in Cohort 2 will be based on data from Cohort 1. A total of approximately 90 adult subjects (18 per arm) between the ages of 18-75 years with well-controlled, biopsy-confirmed CeD and 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), and a third dose of TAK-101 IV infusion will be administered at Week 24. For the third dose, all randomized subjects in all cohorts will receive the same dose of TAK-101 they received with initial treatment, and all subjects initially randomized to placebo will receive a dose of TAK-101 based on the group they are randomized into. Approximately 45 subjects will be randomly assigned into 1 of 3 treatment groups with a 1:2:2 randomization ratio in the first study cohort:

- Group A: Two infusion doses of placebo, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.
- Group B: One infusion dose of 25 µg/kg GE TAK-101 on Day 1 followed by 1 infusion dose of placebo on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.
- Group C: Two infusion doses of 25 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.

After approximately two-thirds of subjects in Cohort 1 have baseline results available and at least 30 subjects have completed Visit 5 liver tests or have early terminated by Visit 5, a safety interim analysis (IA) is planned when 30 subjects reach the primary endpoint on Day 20 of Cohort 1. After a review of Cohort 1 data, a decision will be made either to stop the study or continue the

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study by dosing the second study cohort (ie, Cohort 2). This decision will be made by the sponsor study team, based on the recommendations of the study's IDMC.

If it is deemed appropriate to enroll both the TAK-101 50 µg/kg GE and the 12.5 µg/kg GE dose levels in Cohort 2:

Cohort 2 will consist of 45 subjects randomly assigned to 1 of 3 treatment groups with a 1:2:2 randomization ratio:

- Group A: Two infusion doses of placebo, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 25 µg/kg GE TAK-101 at Week 24.
- Group D: Two infusion doses of 50 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 50 µg/kg GE TAK-101 at Week 24.
- Group F: Two infusion doses of 12.5 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 12.5 µg/kg GE TAK-101 at Week 24.

If it is decided to include 12.5 µg/kg GE but not the 50 µg/kg GE dose level in Cohort 2:

Cohort 2 will consist of 27 subjects randomly assigned to 1 of 2 treatment groups with a 1:2 randomization ratio:

- Group E: Two infusion doses of placebo, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 12.5 µg/kg GE TAK-101 at Week 24.
- Group F: Two infusion doses of 12.5 µg/kg GE TAK-101, 1 infusion dose on Day 1 and 1 infusion dose on Day 8, followed by 1 infusion dose of 12.5 µg/kg GE TAK-101 at Week 24.

If neither 50 µg/kg GE and 12.5 µg/kg GE is recommended to be tested, the study will terminate enrollment. Treatment details are summarized under Table 6.a.

In addition, the IDMC will review safety and laboratory data from the third infusions given to the first 5 subjects and, if needed, the IDMC will make recommendations as appropriate.

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Table 6.a Dose and Regimen

Treatment Groups	Dose 1 (Day 1, Week 0)	Dose 2 (Day 8, Week 1)	Dose 3 (Day 168 + 6, Week 24)	Contingencies	Treatment Description [a]
Group A (Cohort 1 & 2)	Placebo	Placebo	TAK-101 25 µg/kg GE	NA	0.9 % sodium chloride injection infusion on Days 1 and 8 followed by 25 µg/kg GE TAK-101 at Week 24.
Group B (Cohort 1)	TAK-101 25 µg/kg GE	Placebo	TAK-101 25 µg/kg GE	NA	TAK-101 25 µg/kg GE infusion on Day 1 followed by 0.9% sodium chloride injection infusion on Day 8 followed by 25 µg/kg GE TAK-101 at Week 24.
Group C (Cohort 1)	TAK-101 25 µg/kg GE	TAK-101 25 µg/kg GE	TAK-101 25 µg/kg GE	NA	TAK-101 25 µg/kg GE infusion on Days 1 and 8 followed by 25 µg/kg GE TAK-101 at Week 24.
Group D (Cohort 2)	TAK-101 50 µg/kg GE	TAK-101 50 µg/kg GE	TAK-101 50 µg/kg GE	Initiated based on cohort 1 safety data	TAK-101 50 µg/kg GE infusion on Days 1 and 8 followed by 50 µg/kg GE TAK-101 at Week 24.
Group E (Cohort 2)	Placebo	Placebo	TAK-101 12.5 µg/kg GE	Initiated if cohort 1 (25 µg/kg GE) shows activity AND it is decided not to study the 50 µg/kg GE dose level	0.9 % sodium chloride injection infusion on Days 1 and 8 followed by 12.5 µg/kg GE TAK-101 at Week 24.
Group F (Cohort 2)	TAK-101 12.5 µg/kg GE	TAK-101 12.5 µg/kg GE	TAK-101 12.5 µg/kg GE	Initiated if cohort 1 (25 µg/kg GE) shows activity	TAK-101 12.5 µg/kg GE infusion on Days 1 and 8 followed by 12.5 µg/kg GE TAK-101 at Week 24.

GE: gluten epitopes; NA: not applicable.

[a] All randomized subjects who receive the third dose will receive the same dose of TAK-101 they received with initial treatment.

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Subjects aged 18 to 75 years, inclusive, with documented history of biopsy-confirmed CeD, which is well-controlled and on a GFD for a minimum of 6 months, will be screened for enrollment. 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 confirm 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), and 1 IV infusion dose at Week 24. Subjects will be randomly assigned to receive placebo and/or TAK-101 at doses of 25 µg/kg GE in the first study cohort. In the second study cohort, subjects will be randomly assigned to receive placebo and/or TAK-101 at a doses of either 50 µg/kg GE or 12.5 µg/kg GE. For both study cohorts, the maximum dose of TAK-101 to be administered will be 6250 µg GE per dose. Randomization will be stratified based on HLA Class II:

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.

HLA distribution will be monitored throughout the study and enrollment of subjects in certain strata may be limited in order to reflect the known distribution of HLA types in the CeD population.

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 3 single-day 3 g gluten challenges at Weeks 8, 14, and 20. With the exception of these series of gluten challenges, subjects will be required to continue to follow a GFD throughout the duration of the study.

Subjects in all cohorts will be given a single dose of active treatment with TAK-101 after the Week 20 gluten challenge. For the third dose, all randomized subjects will receive the same dose of TAK-101 that they received with initial treatment, and all subjects initially randomized to placebo will receive 25 µg/kg GE TAK-101 or 12.5 µg/kg GE TAK-101, if it is decided not to include the 50 µg/kg GE dose level in Cohort 2.

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Subjects will be observed for TEAEs, including IRRs, potential allergic reactions, and drug-induced CRS, for 2 hours following each study drug infusion. Subjects will be assessed regularly for safety and tolerability by TEAEs, physical examination, vital signs, and routine clinical laboratory tests (chemistry, liver tests, and hematology).

Samples will be collected for safety-related endpoints and monitoring for AESIs. To understand drug activity, samples will be taken to measure the number of gliadin-specific T cells, changes in blood cell immunophenotyping for gut-homing CD4, CD8, and γδ cells, IL2 levels, and PK assessments will be collected as specified in the Schedule of Study Procedures (Appendix A).

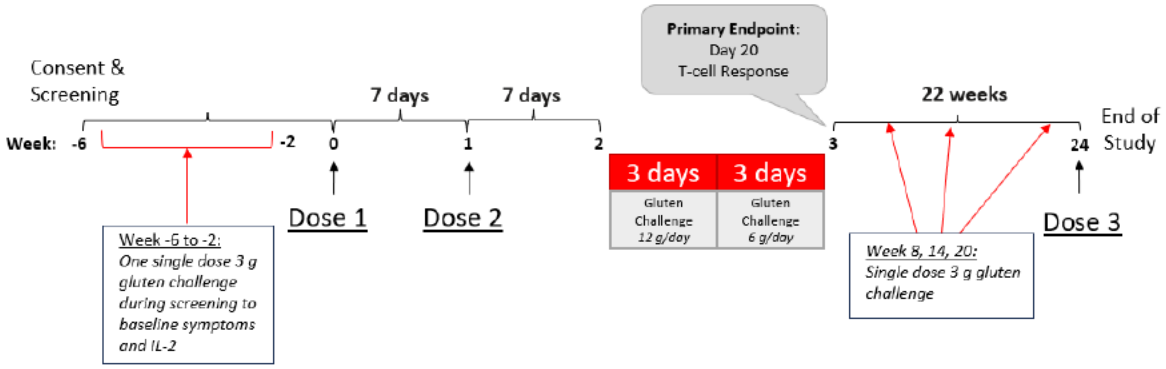
Sites will employ all efforts to see subjects as described in the clinical assessments. In unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, exceptions may be granted for out of window visits and/or alternative methods for conducting subject visits with approval by the medical monitor and/or sponsor. Such instances will be documented in the study records. The 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 the last subject has completed all procedures and assessments or discontinued the study early. After final database lock, the study will be unblinded and a clinical study report will be prepared.

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.

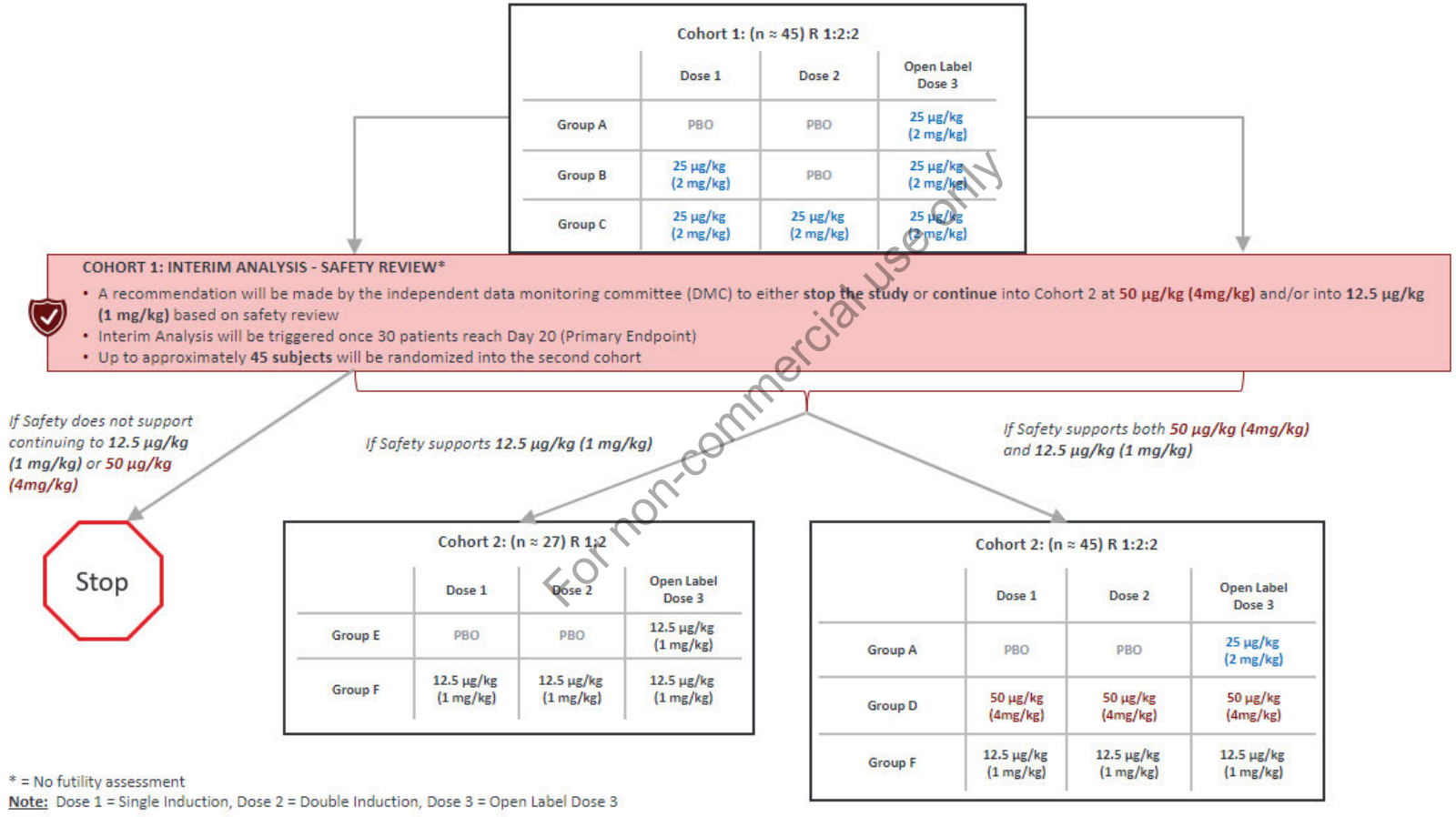
Figure 6.a Schematic of Study Design



IL-2: interleukin-2.

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Figure 6.b Schematic of Study Cohorts: Initial Dosing Regimens



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PBO: placebo; R: randomization.
All subjects will have two doses for efficacy and the third dose will be for safety.

6.2 Justification for Study Design, Dose, and Endpoints

The study population consists of subjects with biopsy-confirmed, asymptomatic CeD (defined as mild or with no ongoing signs or intermittent symptoms felt to be related to active CeD) and following a GFD for at least 6 months. This study population reflects a population most likely to respond to a gluten challenge.

It has been shown in the phase 2a study that TAK-101, given as 100 µg/kg GE twice with 7 days between doses, effectively suppressed T cell activation triggered by gluten challenge compared with placebo. Clinical safety data showed that TAK-101 was well tolerated, most TEAEs were of mild to moderate intensity, and no SAEs were reported. The totality of data supports further development of TAK-101.

Given that nonclinical data has shown reversible hepatotoxicity in 2 animal species at higher doses of TAK-101 and that pharmacologic mouse models suggest that TAK-101 may be effective at doses below the 100 µg/kg GE used in the prior phase 2 study, evaluation of lower doses of TAK-101 is warranted at this phase of development. Therefore, in the current study, lower dose levels of 25 µg/kg GE, 12.5 µg/kg GE (if included based on recommendation from the IDMC) and 50 µg/kg GE will be studied sequentially to explore the active dose range of TAK-101 based on T cell response. In addition, the maximum dose cap has been reduced to 6250 µg GE per infusion from the previous maximum dose cap of 8125 µg GE that was used in the phase 2a study given the reduction in µg/kg GE dosing.

The decision to include the 50 µg/kg GE and/or 12.5 µg/kg GE dose will be based on review of Cohort 1 safety data, and Visit 5 liver tests or early terminated Visit 5.

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6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Study Stopping Rules

The study stopping rules will be used to trigger IDMC review. Based on events observed, dosing may be temporarily stopped pending IDMC review. IDMC review of event-based data will occur within 3 working days of sponsor awareness of triggering events.

- IDMC review will be triggered by the following observations:
  - Any death, where the attribution to study drug cannot be definitively excluded.
  - Any ≥ Grade 3 SAEs with an unacceptable outcome (eg, irreversible injury) where the attribution to study drug cannot be definitively excluded.
  - ≥ 2 subjects experience ≥ Grade 3 AEs in the same system organ class which are not consistent with gluten exposure based on symptomatology and timing related to study gluten exposure.
  - Any Common Terminology Criteria for Adverse Events (CTCAE) v5 Grade ≥ 4 AE where the attribution to study drug cannot be definitively excluded.
  - IRR: Any ≥ Grade 3 IRR with an unacceptable outcome (eg, irreversible injury).

  - Confirmed or suspected allergic/hypersensitivity reaction: Any ≥ Grade 3 acute allergic reaction (AAR) and/or if two or more subjects are confirmed based on symptoms and laboratory values to have an allergic/hypersensitivity reaction.
  - Clinically significant drug-induced liver injury; (laboratory confirmed aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≥ 3 × upper limit of normal [ULN]) in the presence of a total bilirubin more than 2 × ULN.
  - Deep vein thrombosis, pulmonary embolism, and cerebrovascular accident.
- IDMC review will include scheduled assessments of rate of TEAE in placebo versus active treatment. If there are 20% greater TEAEs in the treatment arm, this will be reviewed by the IDMC and the IDMC will make a recommendation regarding study modifications.

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 Good Clinical Practice (GCP), protocol, or contractual agreement, unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

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

The study may be prematurely terminated or suspended in the event of any significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

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. Intermittent symptoms would not exclude subjects from participation as long as symptoms are generally well controlled in the opinion of the

investigator, and as long as symptoms are back to baseline for 2 weeks before the run-in gluten challenge.

2. The subject must be able to maintain a GFD to the best of their capability for ≥6 months.
3. The subject must be HLA-DQ2.5 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 ICF.
7. The subject weighs at least 40 kg and has a body mass index (BMI) between 16 and 40, 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 (ie, condom with or without spermicide)* from signing of ICF throughout the duration of the study and continuing for 100 days after the last dose. The female partner of a male subject should also be advised to use a highly 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 method of contraception* from signing of ICF throughout the duration of the study and continuing for 40 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.

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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) or 5 half-lives, whichever is longer, before signing of the ICF.
2. Has received TAK-101 in a previous clinical study.
3. The presence of other inflammatory GI disorders or systemic autoimmune diseases that either have the potential to cause persistent GI symptoms similar to CeD or are not well controlled without the use of excluded medications.
   - Examples of conditions that are exclusionary include: inflammatory bowel disease, eosinophilic gastroenteritis or colitis, and microscopic colitis requiring treatment in the 6 months before screening.

- Examples of conditions that may be permissible after discussion with the medical monitor/or sponsor include: systemic autoimmune disease such as scleroderma, psoriatic or rheumatoid arthritis, lupus that is stable and without GI involvement, well-controlled autoimmune thyroid disease, well-controlled type 1 diabetes or proton pump inhibitor-responsive eosinophilic esophagitis in symptomatic and histologically confirmed remission.

4. Has known or suspected refractory CeD or ulcerative jejunitis.
5. Has known or suspected allergy to wheat, such as hypersensitivity and/or anaphylaxis including WDEIA. If there is a possible history of urticaria, angioedema, or anaphylaxis to wheat, investigators should perform testing for wheat anti-IgE antibodies or refer to an allergist for evaluation prior to enrollment to rule out any of these allergies.
6. 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 clinically significant liver disease or positive test result 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).

8. Has baseline ALT or AST >1.5 × the ULN, or total bilirubin >1.5 × the ULN unless subject has known Gilbert's syndrome that can explain the elevation of bilirubin.

    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 result at screening or lactating or intends to become pregnant before participating in this study, during the study, and within 40 days after last dose of the study drug; or is not willing to use study-recommended contraceptive measure; or intends to donate ova during such time period.

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12. The subject intends to donate sperm during the course of this study or within 100 days thereafter.
13. Has a history of substance 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 an ongoing infection such as COVID-19 at the time of screening (additional testing may be performed at the discretion of the investigator).
16. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (ie, 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.
18. History of previous thromboembolic events or active bleeding disorders.
19. Has intolerable symptoms after the run-in gluten challenge and is unwilling to undergo subsequent post treatment gluten challenges.
20. Has known allergy to or intolerance of TAK-101 or any of its ingredients or excipients (as referenced in Section 4.1.2). Also, any subject with a symptomatic allergic reaction that is confirmed by laboratory serology such as elevated tryptase levels (refer to Appendix N) following the administration of TAK-101 will be excluded from future dosing.
21. Has a current diagnosis of active malignancy or malignancy diagnosed in the 5 years prior to screening or is receiving ongoing treatment for malignancy (hormone therapy alone is not exclusionary).

    Note: Subjects with fully resected stage 0 (carcinoma-in-situ) or stage 1 tumor without signs of recurrence may participate.

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7.3 Excluded Medications

All prior and concomitant medications taken within 6 months, including prescription and nonprescription medicines, and vaccines must 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 immunosuppressants, corticosteroids, or digestive enzymes, including over-the-counter (OTC) supplements advertised as for digestion of gluten or protection from gluten exposure. Subjects should not start new medications during the duration of the trial without approval of the medical monitor and/or sponsor unless these medications are urgently required per investigator's decision. If this is urgently necessary, please notify sponsor afterwards.

7.4 Diet, Fluid, Activity Control and Treatment Facilities

All subjects will undergo a single-day 3 g gluten challenge at run-in (Week -4, 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 through assessment of T cell activation. Single day 3 g gluten challenges will be administered at the site of blood testing either at home or at clinic. By the end of the study, the subject will have four 3 g/day, three 6 g/day, and three 12 g/day gluten challenges (approximately 66 g of gluten consumed in total through the duration of the 24-week trial). The first dose of the 6-day gluten challenge will be administered in the clinic and the following 5 days of the gluten challenge will be administered at home. Exceptions can be made on a case-by-case basis by sponsor for gluten challenge to be administered at clinic.

Gluten, the challenge agent, will be provided in powder form (vital wheat gluten) and consumed in a single meal mixed with a liquid the patient normally consumes. Please refer to the Pharmacy Manual for further information.

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

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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 that are labeled as "gluten-free."

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 9.1.16 of the protocol.

1. TEAEs:
   - Subjects who experience a TEAE may require early discontinuation if continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the TEAE.

   - Allergic reaction:
     - Subjects who experience Grade 3 or higher AAR on the first infusion will not receive a second infusion.

   - IRRs:
     - Subjects who experience an NCI CTCAE Grade 4 IRR on the first infusion will not receive a second infusion. Subjects who experience an NCI CTCAE Grade 3 IRR on the first infusion may be pretreated with diphenhydramine 30-60 minutes before subsequent doses.

   - Liver findings:
     - LFTs are done at baseline and then repeated at all visits and on Day 2 [±1] postdose for all subjects.
     - To be eligible for the second study drug infusion on Day 8, and any subsequent dosing, liver enzymes/bilirubin must be ≤2 × ULN.
     - Subjects whose liver enzymes/bilirubin do not meet any of the above criteria, repeat testing may be performed at the investigator's discretion, 1 to 2 weeks later. If the results of the repeated testing still do not meet any of the above criteria, the subjects will not receive further study drug infusions and should be monitored/treated according to local standard of care.
     - For subjects with treatment emergent LFT elevations, see Appendix E for additional monitoring, evaluation, and follow-up recommendations.
     - Hepatotoxicity will continue to be evaluated through the clinical development program to further understand and characterize this risk.
2. Significant protocol deviation as defined by the sponsor. 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.

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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 from the study 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. AE leading to discontinuation.
5. Death.
6. 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. Subjects who discontinue or are withdrawn after randomization will not be replaced.

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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. For further information, please refer to the Pharmacy Manual.

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

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8.1.1.1 TAK-101 DP

The sponsor will supply TAK-101 DP to the study site in an open-label manner. TAK-101 DP is a lyophilized powder in a glass vial containing approximately 1250 µg GE (100 mg NP) of TAK-101 with cryoprotectant excipients (sucrose and mannitol). TAK-101 DP 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 USP (normal saline). The 0.9% sodium chloride will be sourced by the study sites to prepare for placebo.

8.1.1.3 Rescue Medications

In some cases, study subjects may have severe reactions to study given gluten that necessitates treatment. The most common symptoms 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 (ie, any corticosteroids, including budesonide).

Medications which may be considered for use as rescue for the symptoms associated with the gluten challenge include 5-HT3 antagonists such as **ondansetron**, GI antispasmodics such as **dicyclomine**, antidiarrheal agents such as **loperamide**, and sympathomimetic agonists such as **epinephrine**. Any exceptions to these rescue medications will require medical monitor and/or sponsor approval unless these medications are urgently required per investigator's decision. If this is urgently necessary, please notify sponsor afterwards.

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 challenge related symptoms should be documented within the eCRF.

8.1.2 Storage

TAK-101 vials must be stored at 2°C to 8°C (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

Important: ***The Hemo-Nate© 18-micron blood filter must be used for administration. Inversion of the infusion bag at the beginning and every 30 minutes until the administration is complete and gently squeezing the infusion port during infusion is required to avoid settling of the particles. Failure to follow these instructions could result in increased treatment emergent adverse events (TEAEs)***.

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

- 40 mL per hour for 30 minutes (~20 mL), then
- 80 mL per hour for the next 30 minutes (~40 mL), then
- 160 mL per hour for the remainder of the infusion (~160 mL).

The total infusion volume will be approximately 230 mL over a total infusion time of approximately 2 hours.
Once the site staff has completed checking patient vitals and mixing the infusion bag (for more information - please refer to Section 10.5.2.2.1), they can increase the infusion escalation rate. The site should check the infusion pumps at regular intervals to ensure that the infusion is being administered to the subject, as planned. Once the site staff has completed checking patient vitals and mixing the infusion bag at the expected 30-minute time interval, they can then proceed to increase the infusion escalation rate. Subjects should avoid vigorous exercise for at least 2 hours before and after the infusion. Additional instructions will be provided in the pharmacy manual.

Please note: TAK-101 DP is an opaque milky white suspension once reconstituted and diluted, and the placebo is a clear solution (normal saline). Both of the IV bags containing TAK-101 DP or placebo and IV tubing will be covered at the time they leave the pharmacy and remain covered throughout treatment administration.

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

Table 8.a Dose and Regimen

Treatment Groups	Dose 1 (Day 1, Week 0)	Dose 2 (Day 8, Week 1)	Dose 3 (Day 168 + 6, Week 24)	Contingencies	Treatment Description [a]
Group A (Cohort 1 & 2)	Placebo	Placebo	TAK-101 25 µg/kg GE	NA	0.9 % sodium chloride injection infusion on Days 1 and 8 followed by 25 µg/kg GE TAK-101 at Week 24.
Group B (Cohort 1)	TAK-101 25 µg/kg GE	Placebo	TAK-101 25 µg/kg GE	NA	TAK-101 25 µg/kg GE infusion on Day 1 followed by 0.9% sodium chloride injection infusion on Day 8 followed by 25 µg/kg GE TAK-101 at Week 24.
Group C (Cohort 1)	TAK-101 25 µg/kg GE	TAK-101 25 µg/kg GE	TAK-101 25 µg/kg GE	NA	TAK-101 25 µg/kg GE infusion on Days 1 and 8 followed by 25 µg/kg GE TAK-101 at Week 24.
Group D (Cohort 2)	TAK-101 50 µg/kg GE	TAK-101 50 µg/kg GE	TAK-101 50 µg/kg GE	Initiated based on cohort 1 safety data	TAK-101 50 µg/kg GE infusion on Days 1 and 8 followed by 50 µg/kg GE TAK-101 at Week 24.
Group E (Cohort 2)	Placebo	Placebo	TAK-101 12.5 µg/kg GE	Initiated if cohort 1 (25 µg/kg GE) shows activity AND it is decided not to study the 50 µg/kg GE dose level	0.9 % sodium chloride injection infusion on Days 1 and 8 followed by followed by 12.5 µg/kg GE TAK-101 at Week 24.
Group F (Cohort 2)	TAK-101 12.5 µg/kg GE	TAK-101 12.5 µg/kg GE	TAK-101 12.5 µg/kg GE	Initiated if cohort 1 (25 µg/kg GE) shows activity	TAK-101 12.5 µg/kg GE infusion on Days 1 and 8 followed by 12.5 µg/kg GE TAK-101 at Week 24.

GE: gluten epitopes; NA: not applicable.

[a] All randomized subjects who receive the third dose will receive the same dose of TAK-101 they received with initial treatment.

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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 the maximum scheduled dose being used in this study (6250 µg GE TAK-101) irrespective of the subject's assigned dose 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 considered AEs and must be

captured as an AE in the AE eCRF(s). 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 treatment group allocation and medication identification number(s) 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) and Visit 10 (Day 168±6, Week 24), the investigator or designee will again access the IRT to request additional study drug for each subject. The treatment allocation and medication identification number(s) of the study drug to be dispensed will be provided by the IRT.

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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 assignments 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.

Please note: TAK-101 DP is an opaque milky white suspension once reconstituted and diluted, and the placebo is a clear solution (normal saline). Both of the IV bags containing TAK-101 DP or placebo and IV tubing will be covered at the time they leave 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 breaking the blind. 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 and/or sponsor 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 before 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.

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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, the sponsor 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.

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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 enters 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) GI 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 baseline assessment before the first dose examination.

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9.1.4 Vital Sign Procedure

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

When vital signs are scheduled at the same time as blood sampling, please collect both the vital signs and blood samples with a gap of 30 minutes between each other.

Weight and height measurements should be recorded at screening (Week -6) and before the third infusion. A subject should have weight and height measured while wearing indoor clothing and with shoes off per standard of care. 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: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Please note the maximum BMI allowed is 40.

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 in HLA-DQ2.5–positive subjects 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 that is used in addition to the study drug during the study period. 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 (any time from signing of ICF until end of the study), and all medication including vaccinations, vitamin supplements, OTC medications, oral herbal preparations and rescue medications 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 ICF. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at the screening/baseline examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be documented.

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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
Glycosylated hemoglobin	Total and direct bilirubin	Leukocytes
Hematocrit	Glucose	Blood
Platelets	Total protein	Bilirubin
Coagulation (D-dimer, PT, PTT, fibrinogen, prothrombin fragment F1+2, and thrombin-antithrombin complex)	Creatinine	Urobilinogen
	Blood urea nitrogen	Ketone
	Creatine kinase	Creatinine
	GGT	
	Potassium	
	Sodium	

Other:

Whole Blood:
Testing for HLA-DQ2.5/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) [b]	
Wheat IgE	
C-reactive protein	
Sample for CRS	
Tryptase	

ALT: alanine aminotransferase; ALP: alkaline phosphatase; anti-HBcAb: antibody to hepatitis B core antibody; AST: aspartate aminotransferase; CRS: cytokine release syndrome; 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; IgE: immunoglobulin E; 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.

[b] Other anti-DGP isotypes may be assessed as per the exploratory endpoints (see Section 5.2.3).

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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 the 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 ICF, throughout the duration of the study, and for 100 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 specified time 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 contraception below.

9.1.9.2 Female Subjects and Their Male Partners

From signing of ICF, throughout the duration of the study, and for 40 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 method of contraception (from the list below).

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

Highly effective contraception methods are defined as < 1% failure rate per year when used consistently and correctly. In this study, the minimum required level of contraception is highly effective contraception. Table 9.b lists of highly effective methods of contraception:

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Table 9.b Acceptable Contraception Methods and Lactation Guidance for This Study

Highly Effective Contraceptives **Failure rate of <1% per year when used consistently and correctly**
User Dependent
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[a,b] – Oral. – Intravaginal. – Transdermal. • Progestogen only hormonal contraception associated with inhibition of ovulation. – Oral. – Injectable. • Sexual abstinence. [c] • Refraining from donating sperm. [f]
Low User Dependency
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation. [a,b] • IUD. • IUS. • Bilateral tubal occlusion. Vasectomy; vasectomized partner. [d,e]
Measures Intended to Prevent Fetal and Neonatal Exposure via Sperm or Breastmilk
• Subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penilevaginal intercourse or use a male condom during each episode of penile penetration 40 days after the last dose. • Subjects who are lactating must agree not to use their breastmilk to feed an infant.

IUD: intrauterine device; IUS: intrauterine hormone-releasing system

[a] Hormonal contraceptives must be stabilized for at least 30 days before the start of the screening period.

[b] Hormonal contraception may be susceptible to interaction with any study treatment, which may reduce the efficacy of the contraceptive method. Therefore, 2 highly effective methods of contraception should be used during the treatment period and for at least 40 days after the last dose of study treatment.

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

[d] A vasectomy is a highly effective contraceptive method only if the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

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Table 9.b Acceptable Contraception Methods and Lactation Guidance for This Study

Highly Effective Contraceptives **Failure rate of <1% per year when used consistently and correctly**

[e] For subjects of childbearing ability, having a vasectomized partner is a highly effective contraception method provided that the partner is the subject's sole partner and that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

[f] Refrain from donating sperm for the duration of the study and for 100 days after the last dose of study treatment.

Unacceptable contraceptive methods in any study that requires contraception are displayed in. Table 9.c.

Table 9.c Unacceptable Contraception Methods

Methods that are unacceptable in *any* study requiring contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus) • Spermicides only • Lactational amenorrhea method (LAM) • Use of both female condom and male condom together at the same time
Contraceptives that are effective but have a failure rate of >1% per year when used consistently and correctly are unacceptable in a study requiring *highly effective contraception (ie, <1% failure rate)*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm or sponge with spermicide

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Subjects will be provided with information on highly 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.

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 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?

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, they 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 100 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, ie, after the randomization visit, the pregnancy should be reported immediately, using a pregnancy notification form, to the study medical monitor and sponsor contact listed in Section 1.1.

Should the pregnancy occur during or after administration of blinded study 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 in enrolled subjects, as well as pregnancies in female partners of male subjects enrolled in the study, will be followed up for pregnancy outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted. The live birth should be followed up at least until 12 months post delivery.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded at baseline during the screening visit and then only if any related AEs occur, including IRRs and allergic reactions. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within

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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.d.

Table 9.d Primary Specimen Collection Table

Specimen #	Specimen name in Schedule of Procedures	Primary specimen	Primary specimen derivative	Description of intended use
1	Blood sample for tetramer staining and ELISpot	Blood	PBMC	Biomarker measurements
2	Blood sample for immunophenotyping and stimulation	Blood	Whole blood	Immunophenotyping and ex vivo stimulation
3	Blood sample for RNA	Blood	RNA	Biomarker measurements
4	Plasma sample for protein	Plasma	NA	Biomarker measurements
5	Urine sample for gluten	Urine	NA	Gluten exposure
6	Plasma sample for PK	Plasma	NA	PK measurements
7	Serum sample for immunogenicity	Serum	NA	ADA measurements

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

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9.1.12.1 Blood Sample (PBMC) for Tetramer Staining and ELISpot

PBMCs will be collected before and 5 days after first day of the 6-day gluten challenge, a time point when gluten-specific T cells [redacted] 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 likely trigger the pathology associated with CeD.
- HLA-DQ2.5 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/or of activation, exhaustion and gut homing. Both ELISpot and tetramer assays will only detect T cell responses in subjects who are HLA-DQ2.5 positive.

9.1.12.2 Blood Sample (Whole Blood) for Immunophenotyping and Stimulation

Whole blood will be collected before and at 5 days after the first day of the 6-day gluten challenge. Immunophenotyping whole blood may be done to characterize T cell subpopulations

in all subjects regardless of HLA haplotype and measures change with gluten challenge including T cells with activated, gut homing or [redacted], as well as cells of other lineages.

Whole blood collected at these times may also be used for testing a novel ex vivo stimulation assay that will allow evaluation of gliadin-specific T cells without the need for gluten challenge. This ex vivo IL-2 assay, if performed, will be ad hoc and not necessarily done on all subjects or all samples. Analysis of data received from ex vivo IL-2 assay may be reported separately from CSR.

9.1.12.3 Blood Cell Collection for RNA

The blood samples for RNA 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 necessarily done on all subjects or all samples. Results are not expected to be 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. Additional plasma biomarkers may be assessed in an exploratory manner at the end of the study. If additional plasma biomarkers (other than IL-2) are performed, they will be ad hoc and not necessarily done on all subjects or all samples. Results of any other cytokine analysis are not expected to be included in the CSR.

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9.1.12.5 Urine Sample for Gluten

Urine samples will be collected from subjects and tested for gluten peptides as evidence of gluten exposure. Measurements will be taken at screening, during the run-in period, at randomization, and all other study visits to monitor study procedure related and inadvertent gluten exposure during study participation. During the gluten challenge phase, some urine collections may be done at home or in the clinic. Effort should be made to collect urine within 6-12 hours after gluten exposure.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Plasma for PK Sampling

Blood samples to assess the concentration of gliadin in plasma will be collected at each dosing visit. Plasma PK samples will be collected predose, 30 minutes after start of the infusion, and at end of infusion on dosing 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.

All PK samples will be analyzed using a validated bioanalytical method. Detailed instructions for handling, processing, storing, and shipping of plasma samples will be provided in the laboratory manual.

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 Serum samples collected at this time are combined with [redacted] and may also be used to develop new or refine the present immunogenicity assay. [redacted]

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9.1.15 Patient-Reported Outcomes Instruments

Refer to Appendix A Table A-3 for administration instructions.

9.1.15.1 CDSD v2.1 and Supplementary Questions (24-Hour [redacted])

The CDSD v2.1 is an 8-item, self-administered questionnaire that evaluates the following CeD symptoms: severity of diarrhea, abdominal pain, bloating, nausea, and tiredness, and frequency of bowel movement and vomiting, and a count of form of the bowel movement. Symptom severity is evaluated using 5-point Likert-type scales ([0] none, [1] mild, [2] moderate, [3] severe, and [4] very severe) for all items except for frequency questions relating to stool counts, diarrhea, and vomiting frequency.
The CDSD v2.1 (24-Hour Recall) 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 and is to be completed daily before bedtime.
[redacted]

9.1.15.2 [redacted]

[redacted]

[redacted]

9.1.15.3 [redacted]

[redacted]

9.1.15.4 Additional Exploratory Questions

[redacted]

9.1.15.5 Documentation of Screen Failure

Investigators must account for all subjects who sign ICF.

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 must not be reused.

9.1.16 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 not to be eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

Please refer to the study manual provided.

9.1.17 End of Study and End of Treatment

End of study (EOS): This date would be the last date of study participation (ie, date of last study assessments or data collection, date of withdrawal of consent, or date of PI decision, etc.).

If the last subject completes the study per protocol, this would be entered as the Follow Up visit. Otherwise, this visit should be entered at any point when the subject ends the study.

End of treatment (ET): The date when the subject receives the last dose in the study.

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9.2 Gluten Exposure Compliance

During the 6-day gluten challenge, subjects will consume gluten on the first day (Day 15) in the clinic, and all subsequent gluten consumption will occur at home (Days 16 through 19). On the final day of the gluten challenge (Day 20), subjects will consume gluten either at home before coming to the clinic or in the clinic. Throughout all 6-days, subjects will be required to document the date and time they consumed the gluten in a daily diary. Subjects should consume their gluten in the night of their single-day challenges and 6-day challenge.

In addition, urine samples for assessment of gluten exposure will be collected within 6-12 hours on following days:

- Pre-dose on day 1 of the gluten challenge (Day 15)
- At home (and brought into the clinic) on day 3 of the gluten challenge (Day 17)
- At home (and brought into the clinic) or at the clinic on day 6 of the gluten challenge (Day 20)

Subjects will be instructed to collect urine 6-12 hours after gluten ingestion, if possible. This can most easily be done by eating gluten at night and collecting the first morning void the next day. If evening ingestion of the gluten is too challenging, then subjects can collect urine during the day as long as the urine is collected 6-12 hours after gluten ingestion.

All subjects should be reinstructed about the gluten 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 dispensation records 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 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's safety and overall clinical status. During this contact, the study site physician or other qualified site staff should also at a 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.

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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 necessary.

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 ICF 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.

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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 preexisting condition. (Intermittent AEs for preexisting 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 AE 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 ICF 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 preexisting 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…").

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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 exposure may be anticipated to include signs and/or symptoms of CeD, including GI symptoms and extraintestinal manifestations such as skin rash, headache, fatigue neurological/neurocognitive manifestations, elevation in liver tests, 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 require intervention such as rescue medication use and/or become SAEs. If severe symptoms require use of rescue medications, rescue medication would be considered as a concomitant medication and each episode of rescue medication use would be considered as an AE.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of ICF are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the preexisting 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 preexisting illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are considered PTEs or AEs and will be documented in the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF as additional AEs with the overdose.

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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 AE in which the subject was at risk of death at the time of the AE; it does not refer to an AE 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 AE is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any AE or synonym described in the sponsor Medically Significant AE List (Table 10.a).

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Table 10.a Sponsor Medically Significant AE List

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

AE: adverse event; SAE: serious adverse event.
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 sponsor may be appropriate. Such AEs may require further investigation in order to characterize and understand them (see Section 10.4 and Section 10.5 on how and when they should be reported to sponsor).

10.1.6 Intensity of PTEs and AEs

The different categories of PTE and AE intensity (severity) are characterized according to NCI CTCAE v5.0 (Appendix F), and in addition, liver AEs will be characterized per FDA guidelines (Appendix G).

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.

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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 AE 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 AE/PTE 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 changing the dose of a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken regarding the study drug.
- 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)
- Drug Infusion Interrupted/Delayed – the dose was interrupted due to the particular AE, and then restarted later. If due to an infusion related reaction (IRR), please refer to Section 10.5.1.1.
- Dose Rate Reduced - Infusion rate reduced following a previous dose interruption due to an AE, and full dose required was subsequently administered. If due to an IRR, please refer to Section 10.5.1.1 for more information about IRR.
- Dose Reduced – subsequent dose reduced secondary to a previous AE eg, previous dose was reduced from 25 µg/kg GE to 12.5 µg/kg GE (please consult sponsor and/or study medical monitor before implementation).

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10.1.13 Outcome

- Recovered/Resolved – Subject returned to first (ie, prior) 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 ICF 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 30 days after the last treatment or until resolution of the AE at principal investigator's discretion.

10.2.1.2 PTE and AE Reporting

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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. Nonserious 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 PTE/AE:

- PTE/AE term.
- Start and stop date and time.
- Frequency.
- Intensity.
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study drug (not applicable for PTEs).
- Outcome of PTE/AE.

- Seriousness.

CDSD Version 2.1, [redacted] 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

Clinically significant AESIs (see Section 10.1.5) reported, during the treatment period or the follow-up period, should be recorded in an AESI Form and if it meets the criteria for SAE, it should also be recorded on a serious adverse event (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:

- Clinically significant abnormal laboratory values, as 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.

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

A short description of the SAE and the reason why the SAE 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 Liver Tests

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 sponsor 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 (ie, ECGs, laboratory tests, discharge summary, post mortem 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.

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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 SAE 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 SAEs and 15 days for other SAEs, 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.

10.4 AESIs and Potential Risks with TAK-101 Treatment

For this study, AESIs include:

- IRRs (observed in prior clinical studies),
- hepatotoxicity (reversible liver injury), based on nonclinical data, thrombosis based on nonclinical data, and
- theoretical risk of allergic reactions in subjects with preexisting wheat allergy, hypersensitivity, and/or anaphylaxis including WDEIA,
- platelet count decreased (observed in nonclinical studies but not in prior clinical studies).

Of these AESI, IRR is an ADR and an important identified risk. Hepatotoxicity, Thrombosis and Allergic reactions in patients with preexisting wheat allergy, hypersensitivity, and/or anaphylaxis including WDEIA are considered as important potential risks. There are no identified risks; Platelet count decreased is considered a potential risk. Additional information is provided in Section 10.5.

10.5 Risk Mitigation Measures and Management of Potential Risks with TAK-101 Treatment

10.5.1 Important Identified Risks

10.5.1.1 IRR

IRR is considered an ADR and an important identified risk with the administration of TAK-101. To date in completed studies the following are considered as IRR AEs: rash, flushing, hypotension, hypertension, concentration disturbance, nausea, vomiting, back pain, and visual changes, hyperhidrosis, dizziness, palpitations, chest discomfort, and headache. These IRR AEs have been observed within 5-10 minutes of starting the infusion and resolve with or without intervention within 1 hour.

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According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5, an acute IRR may occur with an infused therapy by a number of mechanisms. IRRs usually represent symptoms occurring in a close timely relationship to an infusion and are not necessarily linked to anaphylaxis or even hypersensitivity.

Most IRRs are characterized by more nonspecific symptoms. For some products, IRRs more frequently occur on initial exposure, and, sometimes, less-frequent or less-severe reactions are observed on re-exposure. An IRR might not represent a contraindication to further exposure depending on the severity and suspected mechanism of the initial IRR.

Data from the completed studies with TAK-101 have shown mild to moderate symptoms of IRR. The reported IRR AEs in the phase 1 study (Study TGLIA-5.001) included the following: pain in extremity, chills, dyspnea, IRR, fatigue, fibrin D dimer increased, rash, hypotension, sinus tachycardia, concentration disturbance, flushing, nausea, vomiting, back pain, tongue geographic, abdominal pain, headache, and visual changes. The phase 2a study (Study TGLIA-5.002) IRR AEs were hyperhidrosis, dizziness, back pain, vomiting, palpitations, chest discomfort, flushing, hypertension, nausea, and headache. IRRs related to TAK-101 generally begin within 5 to 10 minutes after the start of the IV infusion and resolve with or without intervention within 1 hour in most instances, however, there are instances when the event started later during the IV drug administration. In 1 subject, back pain of similar severity occurred with both the first and second infusions of TAK-101 in Part B of the phase 1 study only and were considered as positive re-challenge, and there were others that reported specific IRR events following first dose and reported different IRR events for the second administrations, which are considered as positive re-challenge.

In addition to these symptoms of IRRs related to TAK-101, IRRs in general may include a range of symptoms including headache, nausea, fever or chills, dizziness, flushing, pruritus, chest pain or back pain, allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, tumor pain (onset or exacerbation of tumor pain due to treatment), urticaria (hives, welts, wheals), and vomiting.

Study subjects will be closely monitored for a minimum of 2 hours after dosing; plus, for clinically significant AEs, IV dosing will be paused for at least 2 hours and restarted at a slower rate (25% less) when deemed appropriate by the investigator after subject has recovered following the IV drug interruption. Additionally, epinephrine will be available at the time of dosing for emergency use if needed. If epinephrine is used as part of treatment, subjects will require an additional 6 hours (minimum) monitoring time post epinephrine administration.

10.5.1.1.1 IRR Management Guidelines

There are guidelines in place (Appendix I) to monitor for this risk in the ongoing study and future studies that will allow for characterization of this risk if data become available.

Additionally, the NCI CTCAE grading to be used for this study is in Appendix F.

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10.5.2 Important Potential Risks

10.5.2.1 Hepatotoxicity (Reversible Liver Injury)

Reversible liver injury is considered an important potential risk with the administration of TAK-101 based on nonclinical data in rats and monkeys. See IB Edition 5 Section 6.4.2.1 for more information.

Guidelines for mitigation and management of reversible liver injury:

- Exclude subjects with clinically significant liver disease or ALT/AST/total bilirubin >1.5 × ULN (with the exception of Gilbert's Syndrome) at baseline.
- To be eligible for the second study drug infusion on Day 8, and any subsequent dosing, liver enzymes/bilirubin must be ≤2 × ULN.
- LFTs are done at baseline and then repeated at all visits and on Day 2 (±1) postdose for all subjects.
- In subjects with post infusion liver enzymes/bilirubin that do not meet any of the above criteria, but are within 2.5 × ULN on Day 3 (2 days [±1] postdose infusion), repeat testing may be performed at the investigator's discretion, 1 to 2 weeks later and the next infusion will be given if results of the repeat tests are within allowable limits above.
- Subjects whose liver enzymes/bilirubin do not meet these criteria after repeated testing will not receive further study drug infusions and should be monitored/treated according to local standard of care.

- For subjects with treatment-emergent LFT elevations, see Appendix E for additional monitoring, evaluation, and follow-up recommendations.

10.5.2.1.1 Management Guidelines for Hepatotoxicity (Reversible Liver Injury)

There are additional guidelines in place (Appendix E) to monitor for this risk in ongoing study and future studies, that will allow for characterization of this risk if data becomes available.

10.5.2.2 Thrombosis

Moderate TAK-101-related pulmonary thrombosis with mortality was observed on a single toxicity study in rats receiving TAK-101 at ≥1875 µg/kg GE (HED 300 µg/kg GE) by an 8-hour nonmixed IV infusion.

The most likely hypothesis for the findings in the rat toxicity study is considered to be related to the lack of an in-line filter and the long residence time in the syringe during the 8-hour infusion used in this particular study, resulting in the infusion of larger agglomerated particles or more concentrated particles with increased thrombosis risk. Due to this, mixing the IV bag every 30 minutes throughout dosing to ensure homogenous delivery of TAK-101, and this must be recorded by the sites (see Section 8.1.3). There have been no reported cases of thrombosis in the completed clinical studies to date.

Data from this ongoing Study will be reviewed to determine appropriate future monitoring and management of this risk.

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10.5.2.2.1 Thrombosis management guidelines

There are guidelines in place (Appendix J) to monitor for this risk in ongoing study and future studies, that will allow for characterization of this risk if data becomes available.

10.5.2.3 Allergic Reactions in Patients With Preexisting Wheat Allergy, Hypersensitivity, and Anaphylaxis Including WDEIA

Allergic reaction in patients with preexisting wheat allergy, hypersensitivity, and anaphylaxis including WDEIA is a theoretical important potential risk with the administration of TAK-101. There have been no reported cases in the completed clinical studies to date. There are multiple proteins from wheat which are potential allergens in individuals with wheat allergies. The major allergens that are felt to be gluten-derived are omega 5 gliadin and low molecular weight (LMW) and high molecular weight (HMW) glutenin subunits. Gliadins and glutenins make up approximately 95% of drug substance and are active ingredients of TAK-101.

WDEIA is a rare IgE-mediated hypersensitivity to wheat allergens because IgE antibodies against the wheat allergens are detected in their sera. Within wheat gliadin, O-5-G and HMW-glutenin are found to be the causative allergens; based on this theoretical risk.

Delayed hypersensitivity is a type of hypersensitivity reaction that may occur in the subjects with wheat allergy; therefore, additional risk mitigation plan is provided in case of delayed hypersensitivity reaction in Appendix K.

10.5.2.3.1 Management Guidelines for Allergic Reactions

There are guidelines in place (Appendix K) to monitor for this risk in ongoing study and future studies, that will allow for characterization of this risk if data becomes available.

10.5.2.4 Delayed Hypersensitivity Reactions

Delayed hypersensitivity reactions may occur anytime from 6 hours to 2 weeks post dose. Therefore, subjects will be instructed to pay attention to any reactions consistent with a delayed hypersensitivity reaction (see Appendix R) that may occur after discharge from the study site. In case of unexpected reactions during the above mentioned time frame, the subject should go to nearest emergency room for treatment and then should report the details to the study staff.

10.5.2.4.1 Management of Delayed Hypersensitivity

There are guidelines in place (Appendix L) to monitor for this risk in the ongoing study and future studies that will allow for characterization of this risk if data becomes available.

10.5.3 Identified risks

There are no identified risks for TAK-101.

10.5.4 Potential risks

10.5.4.1 Platelet Count Decreased

Platelet count decreased is a potential risk with the use of TAK-101 based on nonclinical data from rats and cynomolgus monkeys. No clinically meaningful platelet count decreased have been observed in any of the clinical studies thus far. This risk will continue to be monitored in the clinical study and all future clinical development program to better understand and characterize it.

10.5.4.1.1 Management Guidelines

There are guidelines in place (Appendix M) to monitor for this risk in ongoing study and future studies, that will allow for characterization of this risk if data becomes available.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 IDMC

The IDMC is responsible for making recommendations for changes to the study at IA, if appropriate. Details of the IDMC, including meeting frequency, composition, and review, will be captured in a charter prior to the start of the study. Please refer to the IDMC charter for further information.

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11.2 Study Team

The decision to proceed with either dose arm of Cohort 2 will be made by the study team. The study team will review IDMC recommendations, emergent clinical data including all AESI safety data and all the TEAEs noted in the stopping rules in Section 6.3.1, 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 ICF.

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 sponsor 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.

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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 Council 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.)

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.

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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 Randomized Analysis Set will consist of all subjects who were randomized. Subjects will be analyzed according to the treatment they were randomized to.

The full analysis set (FAS) will consist of all randomized subjects who received 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 HLA-DQ2.5-positive 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 measurable 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.

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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 efficacy analysis of the primary endpoint 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 study drug treatment.

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

All statistical tests will be 2-sided hypothesis tests conducted at the 0.05 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 dose 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 arm. 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 TAK-101 dose 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.

- TAK-101 50 µg/kg GE 2 infusions versus placebo.
- TAK-101 25 µg/kg GE 2 infusions versus placebo.
- TAK-101 25 µg/kg GE 1 infusion versus placebo.
- TAK-101 12.5 µg/kg GE 2 infusions 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 treatment group and stratification factor as class variables and baseline IFN-γ SFUs as covariates. The ANCOVA may be repeated with missing endpoint values that will be imputed by multiple imputation among HLA-DQ2.5–positive subjects.

Secondary Efficacy Analyses:

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

The following secondary endpoints are continuous endpoints with a single postbaseline time point and will be analyzed using an ANCOVA model. The model will include TAK-101 treatment group and stratification factor as class variables and baseline IFN-γ SFUs as covariates. Missing values will not be imputed.

- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day average nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly GI symptom severity score (CDSD v2.1, 24-Hour Recall).

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- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20.

Note: Changes in run-in (Visit 2), and Weeks 8,14 and 20 will be calculated using the difference of average scores.

The following secondary endpoints are continuous longitudinal endpoints and will be analyzed by mixed model for repeated measures (MMRM)approach. The model will include fixed effects for the treatment group, visit, treatment–by–visit interaction, and 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. If the model does not converge, additional covariance structure will be used in the order specified in the statistical analysis plan. 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 from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day average nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in 3-day peak nausea severity score measured in CDSD v2.1 (24-Hour Recall).
- Change from run-in (Visit 2) to Weeks 8, 14, and 20 in the pre- to post–gluten challenge change in weekly GI symptom severity score (CDSD v2.1, 24-Hour Recall).
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at run-in (Visit 2) versus Day 15 and Weeks 8, 14, and 20.
- Comparison between the pre-/post–gluten challenge fold change in plasma IL-2 at each of the following time points: run-in (Visit 2), Day 15, and Weeks 8, 14, and 20.

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Note: Changes in run-in (Visit 2), Weeks 8, 14 and 20 will be calculated using the difference of average scores.

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:

[redacted]

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. Any further details are presented in SAP.

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 (version 24.1 or later). 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.

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13.1.7 Immunogenicity Analysis

The presence of antibodies, where detected, will be summarized descriptively by visit and by treatment group. Further details will be provided in the SAP.

13.1.8 Other Analyses

Additional analyses for PRO validation may be analyzed separately.

13.1.9 Interim Analysis

An external IDMC will review the safety data regularly and at an ad hoc basis during the course of the study. Safety information will be presented by each treatment group to the IDMC. The safety information to be presented includes AEs and abnormal laboratory values, with a focus on liver injury and IRRs. After approximately two-thirds of subjects in Cohort 1 have baseline results available and at least 30 subjects have completed Visit 5 liver tests or have early terminated by Visit 5, an IA will be conducted. Based on the IA results, the IDMC (see Section 11.1) will make the recommendation on the dose levels in Cohort 2. To make the recommendation to start Cohort 2, the IDMC will be reviewing all available safety data on all of the subjects in the first cohort. Data on liver enzyme elevation, along with other safety data, will be presented by treatment group. The IDMC may also request additional analyses if they are deemed necessary to make a recommendation.

The IDMC will also review the Day 20 activity data (ELISpot IFN-γ SFUs) from all subjects in the Cohort 1 and will make the recommendation on whether to enroll subjects in the 12.5 µg/kg GE 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.

Optional internal IAs, also as known as administrative IAs, are those analyses that are performed without any intention to stop or alter the trial as a consequence of those analyses. For optional internal IAs, adjustments to significance levels are not required, and results will be carefully interpreted (Williams et al. 1993).

In addition to the IA for the IDMC to review, an optional internal IA will be conducted to assess potential effects of TAK-101 on gluten-induced symptoms and immune biomarkers. The optional internal IA may include exploratory evaluation of PK and ADA. The evaluation may include utilization of the data derived from the CDSDv2.1 3-day average nausea severity score, CDSD v2.1 3-day peak nausea severity score, CDSDv2.1 weekly GI symptom severity score, and plasma IL-2. The optional internal IA will be performed by an internal unblinded team that is independent from the study execution team. This optional internal IA will be conducted after the IDMC IA when Cohort 1 subjects have completed Visit 7 or early terminated. Further details of the optional internal IA, data handling, and result dissemination will be documented within the optional internal IA charter.

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13.2 Determination of Sample Size

The planned sample size is approximately 90 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 50 µg/kg GE), a sample size of 90 subjects (18 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. Assuming 17% of the subjects will drop out or are not HLA-DQ2.5 positive, approximately 90 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. In acknowledgement of hospital, local, state, or national government restrictions

or other site related factors caused by unavoidable circumstances (eg, COVID-19 pandemic) that may prevent onsite monitoring visits; remote visits and remote data verification may be conducted, if possible and if permitted by local standard operating procedures and regulation.

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.

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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. 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.

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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.

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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 study 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).

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

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

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

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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

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Appendix A Schedule of Study Procedures

Table A-1 Schedule of Study Procedures

	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Third Treatment		Early Termination	Telephone Follow-up
	Visit 1	Visit 2 [aψ]	Visit 3	Visit 3.a [aψ]	Visit 4	Visit 4.a [aψ]	Visit 5	Visit 6	Visit 7 [aψ]	Visit 8 [aψ]	Visit 9 [aψ]	Visit 10	Visit 10.a [aψ]		
Day	**-42**	**-28 ± 7**	**1**	**3 ± 1**	**8**	**10 ± 1**	**15**	**20**	**57 ± 4**	**99 ± 6**	**141 ± 6**	**168 ± 6**	**1-3 days after Visit 10**		**30 days after last dose [o]**
Week	**Week -6**	**Week -4**	**Week 0**		**Week 1**		**Week 2**	**Week 3**	**Week 8**	**Week 14**	**Week 20**	**Week 24**			
Assessment															
General Study Conduct															
Informed consent	X														
Inclusion/exclusion criteria	X														
Demographics	X														
Hepatitis/HIV screening	X														
Wheat IgE [p]	X														
Medical history [b]	X														
Medication history	X														
Electrocardiogram	X														
Physical examination	X		X		X							X		X	
Vital signs [c]	X	X	X		X		X	X	X	X	X	X		X	
PTE/AE assessment, Concomitant medications review	X	X	X	X	X		X	X	X	X	X	X		X	X
Clinical laboratory tests (serum, urine, and other)															
Clinical laboratory evaluations (hematology, liver tests, and chemistry) [d]	X		X		X		X					X		X	
Liver, complement, and coagulation tests [e]				X		X							X		
Urinalysis	X		X								X			X	
Pregnancy test (hCG) [g]	X		X		X		X	X	X	X	X	X		X	
Urine drug and alcohol screening [h]	X														
Blood sample for HLA typing	X														

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	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Third Treatment		Early Termination	Telephone Follow-up
	Visit 1	Visit 2 [aψ]	Visit 3	Visit 3.a [aψ]	Visit 4	Visit 4.a [aψ]	Visit 5	Visit 6	Visit 7 [aψ]	Visit 8 [aψ]	Visit 9 [aψ]	Visit 10	Visit 10.a [aψ]		
Day	**-42**	**-28 ± 7**	**1**	**3 ± 1**	**8**	**10 ± 1**	**15**	**20**	**57 ± 4**	**99 ± 6**	**141 ± 6**	**168 ± 6**	**1-3 days after Visit 10**		**30 days after last dose [o]**
Week	**Week -6**	**Week -4**	**Week 0**		**Week 1**		**Week 2**	**Week 3**	**Week 8**	**Week 14**	**Week 20**	**Week 24**			
Drug assignment, administration, and accountability															
Randomization			X												
Study treatment infusion			X		X [i]							X			
Gluten challenge [j]		X					<--- X [k] --->		X	X	X				
PK/Biomarkers															
Blood sample (PBMC) for tetramer staining and ELISpot [l]			X				X	X							
Blood sample for immunophenotyping and stimulation [l]			X				X	X							
Plasma sample for protein [m]		X					X		X	X	X				
Blood sample for RNA [m]		X					X			X	X				
[redacted]															
Blood sampling for complement, histamine, tryptase, and CRS [f]			X		X							X			
Plasma sample for PK [q]			X		X							X			
Urine sample for gluten [r]	X	X	X		X		X	X	X	X	X	X		X	

AE: adverse event; COVID-19: coronavirus disease 2019; CRS: cytokine release syndrome; DGP: deamidated gliadin peptide; ELISpot: enzyme linked immunospot; ET: early termination; hCG: human chorionic gonadotropin; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IRR: infusion-related reaction; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetic; PRO: patient reported outcome; PT: prothrombin time; PTE: pretreatment event; PTT: partial thromboplastin time; tTG: tissue transglutaminase.

[aψ] Visits 2, 3.a, 4.a, 7, 8, 9, and 10.a can occur in the clinic or at home as deemed feasible by the sponsor/site.

[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. Weight and height measurements should be recorded only at screening (Week -6) and before the third infusion at Visit 10.

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Table A-1 Schedule of Study Procedures

	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Third Treatment		Early Termination	Telephone Follow-up
	Visit 1	Visit 2 [aψ]	Visit 3	Visit 3.a [aψ]	Visit 4	Visit 4.a [aψ]	Visit 5	Visit 6	Visit 7 [aψ]	Visit 8 [aψ]	Visit 9 [aψ]	Visit 10	Visit 10.a [aψ]		
Day	-42	-28 ± 7	1	3 ± 1	8	10 ± 1	15	20	57 ± 4	99 ± 6	141 ± 6	168 ± 6	1-3 days after Visit 10		30 days after last dose [o]
Week	Week -6	Week -4	Week 0		Week 1		Week 2	Week 3	Week 8	Week 14	Week 20	Week 24			

[d] Collect before dosing on infusion days (Days 1 and 8, and Week 24). Hematology tests include platelet count and coagulation tests (D-dimer, PT, PTT, fibrinogen, prothrombin fragment F1+2, and thrombin-antithrombin complex). Chemistry, hematology, and liver tests can be collected if required per investigator discretion after infusion days based on if an adverse reaction occurs.

[e] Liver tests will be measured before dosing on Day 8 and repeated at all visits and on 2 days (±1) after each study treatment infusion (may be performed at home or in clinic but will be analyzed by the central laboratory regardless of site of collection). Coagulation tests include plasma levels of D-dimer, PT, PTT, fibrinogen, prothrombin fragment F1+2, and thrombin-antithrombin complex. See Appendix E for details. Complement testing will be completed before and after infusion visits and 2 days (±1) after each study treatment infusion (may be performed at home or in clinic but will be analyzed by the central laboratory regardless of site of collection).

[f] Samples for tryptase, histamine, and complement assessment should be taken predose (within 30 minutes before dosing) and at end of infusion on each study treatment visit (Weeks 0, 1, and 24). Samples for tryptase, CRS, and histamine should be taken at middose and/or post dose, if necessary. Please see Appendix I, Appendix K, and Appendix L for further information regarding IRR and/or allergic reaction.

[g] Serum pregnancy test at Visit 1; all others are urine pregnancy tests.

[h] Positive results will be assessed by the investigator, and exclusion will be based on local regulations and the subject's medical history. Positive cases should be discussed with the medical monitor.

[i] Second infusion may be delayed 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. Refer to Table A-3 for full details on PRO assessments.

[k] On Day 15, the first day 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, the final day 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 Gluten Challenge for more details.

[l] Collection to be done before dosing at Week 0 and before gluten challenge at Week 2, and after gluten challenge at Day 20/Week 3, the final day of the 6-day gluten challenge.

[m] Plasma sample for protein will be collected before and 4 hours after each gluten challenge at run-in and at Weeks 2, 8, 14, and 20. Blood sample for RNA will be collected before and 4 hours after each gluten challenge at run-in and at Weeks 2, 14, and 20.

[n] [redacted].

[o] Subjects who complete an ET visit do not require a telephone follow up.

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	Screening/ Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period					Third Treatment		Early Termination	Telephone Follow-up
	Visit 1	Visit 2 [aψ]	Visit 3	Visit 3.a [aψ]	Visit 4	Visit 4.a [aψ]	Visit 5	Visit 6	Visit 7 [aψ]	Visit 8 [aψ]	Visit 9 [aψ]	Visit 10	Visit 10.a [aψ]		
Day	-42	-28 ± 7	1	3 ± 1	8	10 ± 1	15	20	57 ± 4	99 ± 6	141 ± 6	168 ± 6	1-3 days after Visit 10		30 days after last dose [o]
Week	Week -6	Week -4	Week 0		Week 1		Week 2	Week 3	Week 8	Week 14	Week 20	Week 24			

[p] IgE should only be done (at screening) if wheat allergy is suspected and/or evaluation with allergist is required.
[q] Plasma sample for PK will be taken predose, mid-dose, and after dose for Visit 3. For Visits 4 and 10, these PK samples will be taken at mid-dose and after dose.
[r] Refer to Table A-2.

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Table A-2 Schedule of Study Procedures for 6-Day Gluten Challenge

Follow-up Period						
	Visit 5					**Visit 6**
Day	**15**	**16**	**17**	**18**	**19**	**20**
	Week 2					**Week 3**
Assessment						
Site of gluten challenge [a]	clinic	home	home	home	home	home or clinic
Gluten challenge daily diary [a]	X	X	X	X	X	X
Blood sample for biomarkers [b]	X					X
Urine sample for gluten [c]	X		X [d]			X

[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. If necessary, for Days 16-19, the gluten challenge can also be done in clinic with sponsor approval.

[b] Blood sample will be taken in the clinic.

[c] Urine samples for assessment of gluten exposure will be collected in the clinic on Day 15 of the 6-day gluten challenge (pre gluten challenge), Day 17 at home (first morning void), and Day 20 at home or in clinic (first morning void) (pre–gluten challenge). When possible, urine samples for gluten should be collected 6-12 hours after gluten ingestion.

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

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Table A-3 Schedule of Study Procedures for PROs

	Administration directions	Screening /Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period								Third Treatment		Telephone Follow-up
		Visit 1	Visit 2	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Gluten challenge				Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 10.a	
Day		-42	-28 ± 7	1	3 ± 1	8	10±1	15	16	17	18	19	20	57±4	99±6	141± 6	168± 6	1-3 days after Visit 10	30 days after last dose
Week		Week -6	Week - 4	Week 0		Week 1		Week 2					Week 3	Week 8	Week 14	Week 20	Week 24		
[redacted]																			

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Table A-3 Schedule of Study Procedures for PROs

	Administration directions	Screening /Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period								Third Treatment		Telephone Follow-up
		Visit 1	Visit 2	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Gluten challenge				Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 10.a	
Day		-42	-28 ± 7	1	3 ± 1	8	10±1	15	16	17	18	19	20	57±4	99±6	141± 6	168± 6	1-3 days after Visit 10	30 days after last dose
Week		Week -6	Week - 4	Week 0		Week 1		Week 2					Week 3	Week 8	Week 14	Week 20	Week 24		
[redacted]																			

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Table A-3 Schedule of Study Procedures for PROs

	Administration directions	Screening /Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period								Third Treatment		Telephone Follow-up
		Visit 1	Visit 2	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Gluten challenge				Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 10.a	
Day		-42	-28 ± 7	1	3 ± 1	8	10±1	15	16	17	18	19	20	57±4	99±6	141± 6	168± 6	1-3 days after Visit 10	30 days after last dose
Week		Week -6	Week - 4	Week 0		Week 1		Week 2					Week 3	Week 8	Week 14	Week 20	Week 24		
[redacted]																			

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Table A-3 Schedule of Study Procedures for PROs

	Administration directions	Screening /Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period									Third Treatment		Telephone Follow-up
		Visit 1	Visit 2	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Gluten challenge				Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 10.a	
Day		-42	-28 ± 7	1	3 ± 1	8	10±1	15	16	17	18	19	20	57±4	99±6	141± 6	168± 6	1-3 days after Visit 10	30 days after last dose
Week		Week -6	Week - 4	Week 0		Week 1		Week 2					Week 3	Week 8	Week 14	Week 20	Week 24		
[redacted]																			

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Table A-3 Schedule of Study Procedures for PROs

	Administration directions	Screening /Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period								Third Treatment		Telephone Follow-up
		Visit 1	Visit 2	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Gluten challenge				Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 10.a	
Day		-42	-28 ± 7	1	3 ± 1	8	10±1	15	16	17	18	19	20	57±4	99±6	141± 6	168± 6	1-3 days after Visit 10	30 days after last dose
Week		Week -6	Week - 4	Week 0		Week 1		Week 2					Week 3	Week 8	Week 14	Week 20	Week 24		
[redacted]																			
CDSD v2.1 (24-	Daily in the evening	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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Table A-3 Schedule of Study Procedures for PROs

	Administration directions	Screening /Run-in	Run-in Gluten Challenge	Treatment Period				Follow-up Period								Third Treatment		Telephone Follow-up
		Visit 1	Visit 2	Visit 3	Visit 3.a	Visit 4	Visit 4.a	Visit 5	Gluten challenge				Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 10.a	
Day		-42	-28 ± 7	1	3 ± 1	8	10±1	15	16	17	18	19	20	57±4	99±6	141± 6	168± 6	1-3 days after Visit 10	30 days after last dose
Week		Week -6	Week - 4	Week 0		Week 1		Week 2					Week 3	Week 8	Week 14	Week 20	Week 24		
Hour Recall)	before bedtime																		
[redacted]																			

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CDSD: Celiac Disease Symptom Diary; CeD: celiac disease; [redacted]; [redacted]; PRO: patient-reported outcome.

Early termination visit assessment would include [redacted] and CDSD v2.1 (24-Hour Recall).

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 or equivalent), 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.

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

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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

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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:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) the sponsor, its affiliates, and licensing partners; (2) business partners assisting the sponsor, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, the sponsor will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to the sponsor's research databases for purposes of developing a better understanding of the safety 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;
    d) 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
    e) that the subject's identity will remain confidential in the event that study results are published.

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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 within 100 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.

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Appendix D Investigator Consent to Use of Personal Information

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

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

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

- Assessment of the suitability of investigator for the 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 sponsor, 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 the sponsor and other parties for the purposes described above.

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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.

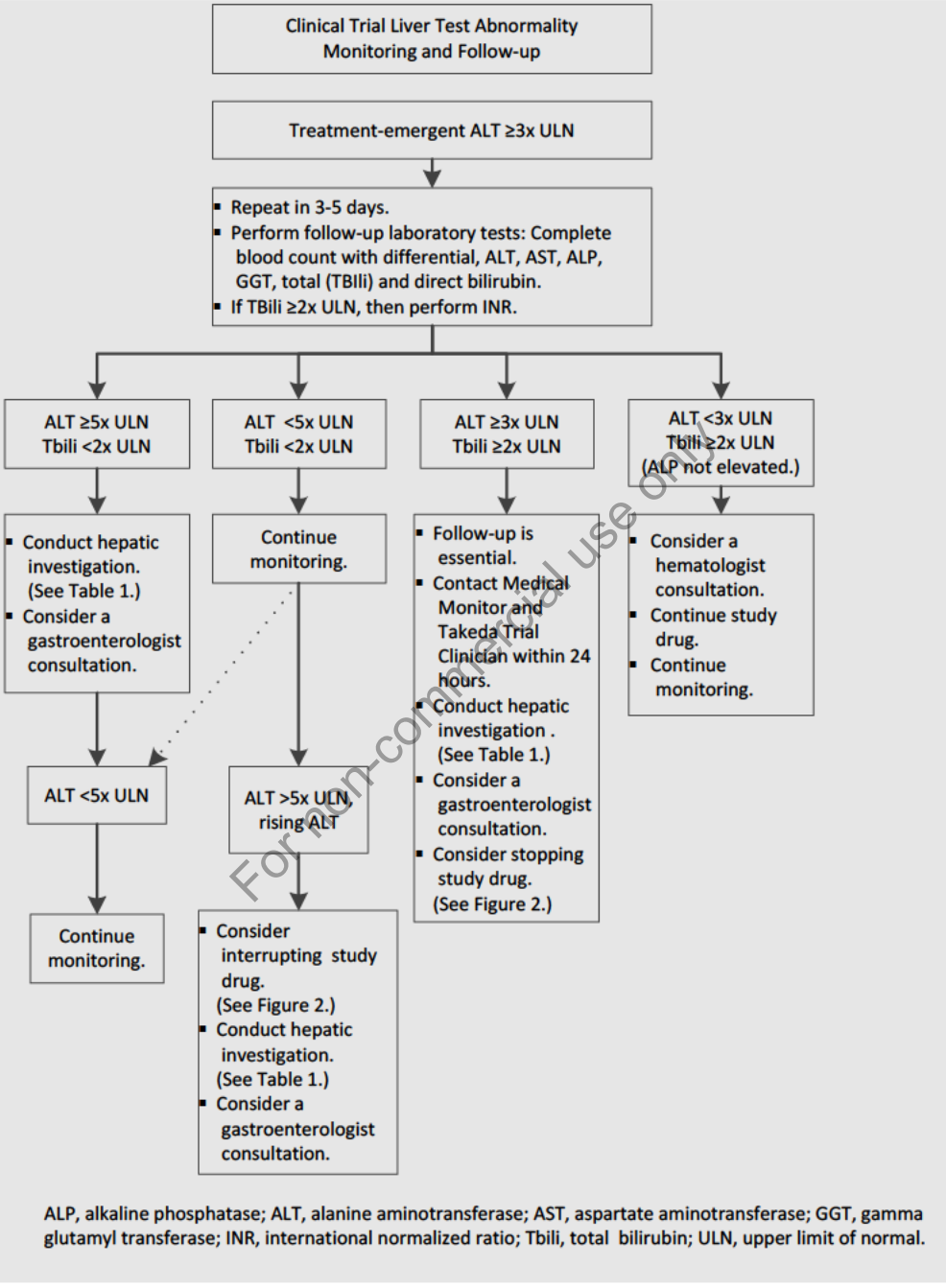
Liver enzymes must be assessed in all subjects after the first infusion and confirmed to be within acceptable range before receiving the second infusion. To be eligible for the second study drug infusion, post first infusion liver enzymes must be confirmed to be ≤2 × ULN.

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 sponsor 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.

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



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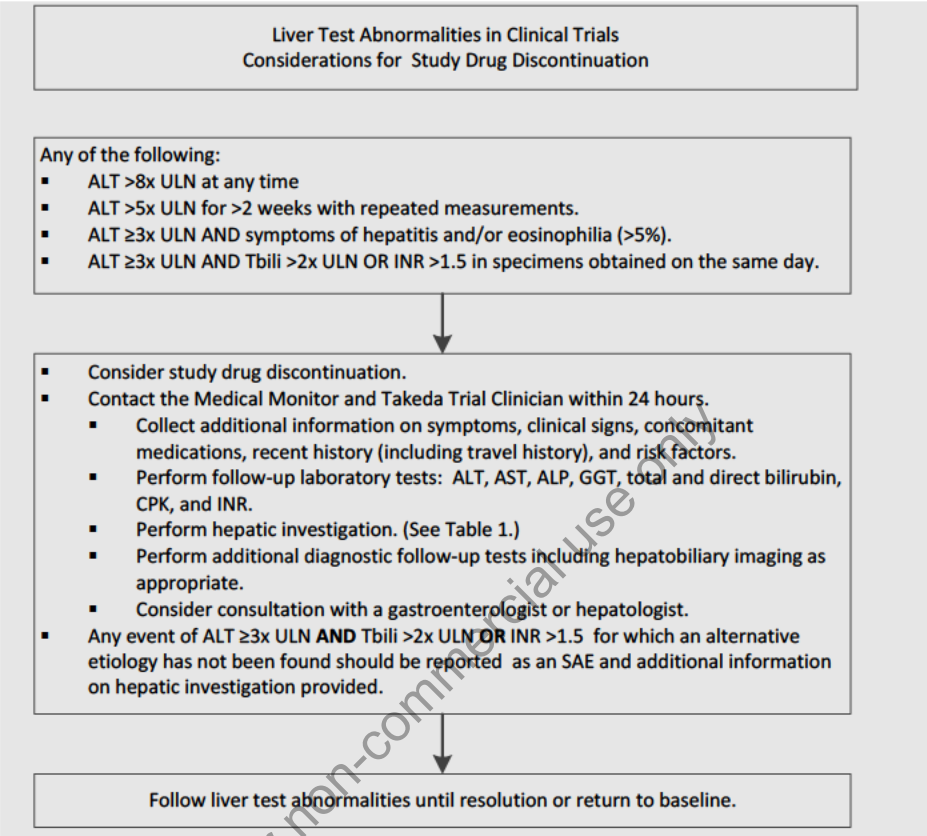
Appendix E Table 1: Hepatic Investigation

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.

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



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

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Appendix G DILI Severity Grading Scales

	US Drug-Induced Livery Injury Network
1: Mild	Elevated ALT and/or ALP but TBL <2.5 mg/dL and INR <1.5.
2: Moderate	Elevated ALT and/or ALP and TBL ≥2.5 mg/dL or INR ≥1.5.
3: Moderate-severe	Elevated ALT, ALP, TBL and/or INR and hospitalization or ongoing hospitalization prolonged due to DILI.
4: Severe	Elevated ALT and/or ALP and TBL ≥2.5 mg/dL and at least 1 of the following: • Hepatic failure (INR >1.5, ascites or encephalopathy). • Other organ failure due to DILI.
5: Fatal	Death or liver transplantation due to DILI.

ALP: alkaline phosphatase; ALT: alanine aminotransferase; DILI: drug-induced liver injury; INR: international normalized ratio; TBL: total bilirubin.

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Appendix H Definition of IRRs, Allergic Reaction, and Anaphylaxis

An acute infusion reaction may occur with an agent that causes cytokine release (for eg, monoclonal antibodies or other biological agents).

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever), arthralgia (joint pain), bronchospasm, cough, dizziness, dyspnea (shortness of breath), fatigue (asthenia, lethargy, malaise), headache, hypertension, hypotension, myalgia (muscle pain), nausea, pruritis/itching, rash/desquamation, rigors/chills, sweating (diaphoresis), tachycardia, tumor pain (onset or exacerbation of tumor pain due to treatment), urticaria (hives, welts, wheals), and vomiting.

Per NCI CTCAE version 5, an allergic reaction is defined as a disorder characterized by an adverse local or general response from exposure to an allergen, while anaphylaxis is defined as a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response, clinically presenting with breathing difficulty, dizziness, hypotension, cyanosis, loss of consciousness, and potentially leading to death.

NCI CTCAE version 5 newly includes separate categories for IRR and CRS. IRR is defined as a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances and CRS is defined as a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath caused by the release of cytokines from the cells. IRRs usually represent symptoms occurring in a close timely relationship to an infusion and are not necessarily linked to anaphylaxis or even hypersensitivity.

However, the majority of IRRs are characterized by more nonspecific symptoms, for some products, more frequently occurring on initial exposure and sometimes less frequent/severe reactions are observed on re-exposure. An IRR might not represent a contraindication to further exposure. A range of symptoms including headache, nausea, fever or chills, dizziness, flush, pruritus, and chest or back pain have been described in relation to infusions. It is acknowledged that the distinction between an IRR and anaphylaxis can be challenging, but nevertheless such distinction is necessary because of the different clinical consequence.

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Appendix I IRR Management Guidelines

Below are the management guidelines to monitor for this risk.

- In the event of an NCI CTCAE Grade 1 or 2 IRR, the infusion should be slowed or stopped at the discretion of the investigator based on clinical presentation. The infusion may be restarted at a slower rate (25% slower than the original rate) after IRR AE resolution.
- In the event of a clinically significant IRR (NCI CTCAE Grade 3), the infusion should be stopped and applicable standard of care should be administered. The investigator/designee should contact the sponsor and study medical monitor. After signs and symptoms of an IRR have resolved, at the discretion of the investigator and based on subject's presentation, the infusion may be restarted at a slower rate (~25% slower than the original rate) after IRR AE resolution. The subjects may be pretreated with diphenhydramine 30 to 60 minutes before the subsequent doses.
- If a severe IRR occurs (NCI CTCAE Grade 3 or 4 signs or symptoms), discontinue TAK-101 infusion permanently and institute treatment as needed and monitor closely according to standard of care. The investigator/designee should contact the sponsor and study medical monitor.
- Of note, for subjects who had dose rate reduced/interrupted secondary to an AE, subsequent infusions should be initiated at or below the reduced dose rate.
- Sites must have epinephrine available on standby before dosing for emergency purposes throughout infusion time until discharge for all subjects (minimum of 2 to 4 hours post dose).
- Additionally, if epinephrine is administered secondary to an AE, the subject will need to be monitored for at least 6 hours before discharge.

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If a subject experiences an IRR of Grade 3 or higher in intensity, the sponsor should be notified at the earliest possible time.

In addition, if a subject experiences an IRR, 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 IRR and at least every 15 minutes until the resolution or stabilization of the IRR.
- Blood samples for histamine, tryptase, C-reactive protein, cytokine release syndrome panel (IFN-γ, IL-1-β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and tumor necrosis factor-α), and C3a, C5a, and sC5b-9 complement levels will be drawn at the time of the IRR.
- The investigator may administer any medically indicated pharmacologic agent or procedure intended to relieve symptoms as specified in the protocol.

Additional instructions

- Signs and symptoms of the IRR and drugs given for treatment of the IRR are to be recorded in the medical record and in the eCRF.
- All changes to infusion rate, including time of pausing and resuming infusion, are to be recorded in the medical record and in the eCRF.

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Appendix J Thrombosis Management Guidelines

In this clinical study, the following management guidelines will be applied:

- Subjects with a history of thromboembolic events or active bleeding disorders will be excluded from the studies.
- As TAK-101 particles may settle and/or theoretically become agglomerated while in the IV administration bag, an in-line filter must be used.
- Mixing of the infusion bag:
  - Site must ensure mixing of TAK-101 during infusion is implemented to prevent potentially agglomerated particles being delivered to patients.
    - Mix the bag every 30 minutes (see below) during the total infusion time.
    - This mixing should be done by inversion and gentle squeezing of the infusion bag at the beginning of infusion and every 30 minutes during infusion to ensure homogenous delivery. This procedure must be appropriately recorded by the sites for each subject in the eCRF for all the times the infusion was mixed. Refer to Section 8.1.3 for details.
- Subjects who develop clinically significant (NCI CTCAE Grade 3 or more) thrombosis during the study will not receive further study drug infusions and will be managed and monitored by the investigator according to the local standard of care, and subjects' outcomes must be recorded in the eCRF.

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Appendix K Management Guidelines for Allergic Reactions

The following risk mitigation and management measures will be implemented:

Delayed hypersensitivity is a type of hypersensitivity reaction that may occur in subjects with wheat allergy; therefore, the additional risk mitigation plan below is provided in case of delayed hypersensitivity reaction.

- Subjects with a history of wheat-related allergy, hypersensitivity, and/or anaphylaxis are excluded from the studies.
- Subjects with uncertainty about previous wheat allergy will be required to consult their allergist to rule out wheat allergy before enrollment in the study.
- Close monitoring at start of dosing through a minimum of 2 to 4 hours post dose is to be implemented for all subjects.
- To reduce the theoretical risk of WDEIA, subjects should be instructed to refrain from vigorous exercise at least 2 hours before and after dosing.
- Sites must have epinephrine available on standby before dosing for emergency purposes throughout infusion time until discharge for all subjects (minimum 2 to 4 hours post dose).
- Additionally, if epinephrine is administered secondary to an AE, the subject will need to be monitored for at least 6 hours before discharge.
- If a subject experiences a Grade 3 or higher acute allergic reaction (Appendix O), then the current infusion will be stopped, further infusions will not be administered, and the subject will be discontinued from the study. Refer to Appendix N and Appendix O for management guidelines.
- If an allergic reaction is suspected, laboratory tests will be done to confirm the occurrence of an allergic reaction. These tests would include the following:
  - Tryptase level (tryptase level of 1.2 × baseline + 2 confirms allergic reaction)
  - Wheat IgE
  - Histamine
  - Eosinophil levels
- If an allergic reaction is suspected, treatment should be given according to Appendix O and/or local standard of care immediately. Any instance of suspected allergic reaction should be discussed with the sponsor and study medical monitor as soon as possible.
- Subjects who meet criteria in Appendix N with laboratory values (tryptase level of 1.2 × baseline + 2) confirming that an anaphylaxis/hypersensitivity reaction has occurred will be discontinued from further study drug administration. However, subjects with Grade 1 and 2 confirmed allergic reactions (Appendix O), if deemed appropriate by the investigator, may receive subsequent dosing following premedication with diphenhydramine 1 to 2 mg/kg at least 30 to 45 minutes before study drug dosing.

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- Delayed hypersensitivity reactions may occur any time from 6 hours to 2 weeks post dose. Therefore, subjects will be instructed to pay attention to any reaction that may occur after discharge from study site. In case of reactions during the above-mentioned time frame, subjects should go to the nearest emergency room for treatment and should report the details to the study staff.
- The management guideline in Appendix O and Appendix P should be followed for all grades of allergic reactions/anaphylaxis/hypersensitivity reactions.

A resting respiratory rate ≥22 breaths/minute in respiratory signs and symptoms, resting heart rate ≥100 beats/minute, and systolic blood pressure ≤90 mmHg are considered as clinically significant vital signs that should trigger intervention for potential hypersensitivity/anaphylaxis.

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Appendix L Management of Delayed Hypersensitivity

Delayed hypersensitivity is defined as allergic reactions occurring from about 6 hours up to 2 weeks post dose. The mean half-life of TAK-101 is between 2 and 4.9 hours; therefore, the risk of a delayed hypersensitivity reaction is expected to be low. However, if any of the symptoms mentioned in Appendix R develop from 6 hours up to 2 weeks post dose, this may be considered as a possible delayed hypersensitivity reaction. Subjects will be given information regarding identification of delayed hypersensitivity reactions at the end of each dosing appointment upon discharge, provided with the telephone number of the site, and instructed to call immediately if any symptoms develop within 2 weeks following study drug administration. Additionally, subjects should go to the nearest emergency room.

Treatment will be based on Appendix R and standard of care at the site and per principal investigator discretion. The sponsor study physicians should be informed as soon as possible by the study site.

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Appendix M Management of Platelet Count Decreased

- Subjects with ongoing bleeding disorders are excluded.
- If a subject develops a clinically significant bleeding disorder after the administration of TAK-101, the subject will not receive further dosing and should be monitored/treated according to local standard of care. The sponsor study physicians should be informed as soon as possible by the study site.

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Appendix N Clinical Criteria for Diagnosing Anaphylaxis Following the Administration of TAK-101

<table>
<tr><td colspan="2">Anaphylaxis is highly likely when any ONE of the following 3 criteria is fulfilled:</td></tr>
<tr><td colspan="2"><u>Criterion One</u></td></tr>
<tr><td>Acute onset of an illness with involvement of the skin, mucosal tissue, or both
(generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
+</td><td>Respiratory compromise
(dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
or
Reduced blood pressure or associated symptoms of end-organ dysfunction
(hypotonia, collapse, syncope, incontinence)</td></tr>
<tr><td colspan="2">OR
<u>Criterion Two</u></td></tr>
<tr><td colspan="2">Two or more of the following:
Occurring rapidly after exposure to TAK-101
(minutes to several hours)</td></tr>
<tr><td>Involvement of the skin-mucosal tissue
(generalized urticaria, itch-flush, swollen lips-tongue-uvula)</td><td>Reduced blood pressure or associated symptoms
(hypotonia, collapse, syncope, incontinence)</td></tr>
<tr><td>Respiratory compromise
(dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)</td><td>Persistent gastrointestinal symptoms
(crampy abdominal pain, vomiting)</td></tr>
<tr><td colspan="2">OR
<u>Criterion Three</u></td></tr>
<tr><td colspan="2">Reduced blood pressure
after exposure to TAK-101
(minutes to several hours)
Systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person’s baseline</td></tr>
</table>

PEF: peak expiratory flow.
Source: (Simons et al. 2015)

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Appendix O Severity Grading System for Acute Allergic Reactions in Adults (AAR Grading)

Severity Grading	Clinical Criteria Subgrading system	Treatment Guidelines
Grade 1	Any mild: Skin, Gastrointestinal, Mucosal/Angioedema	Treat symptomatically as required (eg, H1 blocker)
Grade 2	2 or more mild, any moderate: Skin, Gastrointestinal, Mucosal/Angioedema	Treat symptomatically as required (eg, H1 blocker)
Grade 3	Any mild: Cardiovascular, Neurologic, Respiratory	Use epinephrine 0.3 mg first; H1 blocker can be added on if necessary
Grade 4	Any moderate: Cardiovascular, Neurologic, Respiratory, or Severe Mucosal/Angioedema	Use epinephrine 0.3 mg first; adjunctive therapy of albuterol for chest tightness if needed with any other adjunctive therapy as per standard of care
Grade 5	Any Severe: Cardiovascular, Neurologic, Respiratory	Use epinephrine 0.3 mg first; adjunctive therapy of albuterol for chest tightness if needed with any other adjunctive therapy as per standard of care
Note: Refer to Appendix Q for breakdown of clinical criteria subgrading and Appendix P for detailed treatment guidelines.		
Sources: (Golden et al. 2024) and (Boyce et al. 2010)		

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Appendix P Management Guidelines for Acute Allergic Reactions in Adults if CoFAR Grade 3 and Above Reactions Occur Following the Administration of TAK-101

	Treatment	*Directions*
First line Treatment	Epinephrine IM, 0.3 mg epinephrine autoinjector	Inject into the anterior lateral thigh. Epinephrine dose will need to be repeated every 5-15 minutes.
Adjunctive treatment	1. Albuterol MDI or nebulized solution	8 puffs (MDI) for adults or 3 mL (nebulized) every 20 mins or continuously as needed
	2. Diphenhydramine 1 to 2 mg/kg	Max dose of 50 mg IV or oral liquid
	3. Ranitidine 1 to 2 mg/kg per dose	Max dose of 75 to 150 mg oral and IV
	4. Prednisone 1 mg/kg	Max dose of 60 – 80 mg oral
	5. Methylprednisolone 1 mg/kg	Maximum dose of 60 – 80 mg IV
	6. Vasopressors (other than epinephrine)	Titrate to effect for refractory hypotension
	7. Glucagon 1-5 mg for adults	Titrate to effect for refractory hypotension. Dose can be repeated of 5-15 µg/min
	8. Atropine	Titrate to effect for bradycardia
	9. Supplemental oxygen therapy	
	10. IV fluids	In large volumes if patient presents with orthostasis, hypotension, or an incomplete response to IM epinephrine
	11. Place the patient in recumbent position if tolerated with the lower extremities elevated	

IM: intramuscular; IV: intravenous; MDI: metered dose inhaler.

Source: (Boyce et al. 2010)

Note: These treatments often occur concomitantly and are not meant to be sequential with the exception of epinephrine as first-line treatment.

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Appendix Q Clinical Subgrading for Assessment of Severity of Acute Allergic Reactions (AAR) in Adults

Cardiovascular	Mild: Symptoms = weak, dizzy, presyncope, palpitations, blurred vision. Moderate: hypotension, syncope (collapse). Severe: anaphylactic shock, cardiac arrest.
Neurologic:	Mild: Symptoms = confusion, drowsy, sense of impending doom. Moderate: GCS 13-14. Severe: GCS <13, seizure.
Respiratory:	*General* Mild: Symptoms = chest tightness, dyspnea. Moderate: new-onset persistent cough, increased work of breathing (WOB), hypoxemia. Severe: respiratory failure. *Laryngeal* Mild: Symptoms = throat tightness or discomfort, Signs = voice change. Moderate: stridor without increased WOB. Severe: stridor with increased WOB (partial or complete upper airway obstruction). *Lower airway* Mild: wheezing without increased WOB. Moderate: wheezing with increased WOB. Severe: bronchospasm with minimal or no air movement on auscultation and increased WOB.
Mucosal/Angioedema	Mild: Symptoms = mouth tingling, itchy mouth or throat, metallic taste, Signs = facial swelling; conjunctival infection; chemosis; nasal congestion; rhinorrhea; throat clearing; lip swelling; mild tongue, soft palate, and/or uvula swelling (anatomical landmarks preserved). Moderate: drooling; moderate tongue, soft palate, and/or uvula swelling (anatomical landmarks obscured). Severe: severe tongue, soft palate, and/or uvula swelling (complete loss of anatomical landmarks).

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Skin	*Pruritus* Mild: Symptoms = pruritis, skin discomfort, Signs = occasional scratching, localized scratching or excoriations (<50% body surface area [BSA]). Moderate: continuous scratching, generalized scratching or excoriations (≥50% BSA). *Urticaria* Mild: localized urticaria (<50% BSA), localized erythema (<50% BSA). Moderate: generalized urticaria (≥50% BSA), flushing, and generalized erythema (≥50% BSA).
Gastrointestinal	Mild: Symptoms = nausea, abdominal pain, Signs = 1-2 episodes of emesis or diarrhea. Moderate: Symptoms = frequent or continuous nausea or abdominal pain, distressed due to GI symptoms, Signs = ≥3 episodes of emesis or diarrhea or 2 of each.

Definitions

Hypotension: estimated or calculated mean arterial pressure <65% or systolic BP <90 mmHg or >30% decrease from baseline.

Anaphylactic shock: anaphylaxis with an IV vasopressor infusion requirement to maintain a MAP ≥65 mmHg or systolic BP ≥90 mmHg among adults.

Increased work of breathing (WOB): retractions, use of accessory muscles, nasal flaring, age-defined tachypnea that is not brief or self-resolved.

Hypoxemia: SpO2 ≤ 92% on room air

Respiratory Failure: impaired oxygenation on ventilation requiring use of noninvasive and/or invasive ventilatory support (bag mask ventilation, high-flow nasal cannula, continuous positive airway pressure, bilevel positive airway pressure, mechanical ventilation, extracorporeal membrane oxygenation).

GCS = Glasgow Coma Scale https://www.glasgowcomascale.org/

Source: (Golden et al. 2024)

BP: blood pressure; BSA: body surface area; GCS: Glasgow Coma Scale; GI: gastrointestinal; IV: intravenous; MAP: mean arterial pressure; Spo2: Saturation of peripheral oxygen.

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Appendix R Identification, Monitoring, and Treatment of Delayed Hypersensitivity Reactions

Identification	Rash or other characteristic cutaneous manifestations, such as blisters, mucosal involvement, or facial swelling, or systemic symptoms such as fever or lymphadenopathy that develop greater than 6 hours post dose
Monitoring	Subjects will be educated by the site staff and given identification information to monitor for delayed hypersensitivity reactions. Additionally, subjects will be provided with the telephone number of the site and instructed to call immediately if any delayed hypersensitivity symptoms develop after 6 hours to 2 weeks following their infusion.
Treatment	A complete blood cell count, as well as liver and kidney function tests, should be performed to identify if there is a more severe delayed hypersensitivity reaction ongoing, such as a drug reaction with eosinophilia and symptomatic symptoms. If the typical treatment of cutaneous drug eruptions (maculopapular rash) is confirmed, then the site staff should apply a high-potency topical corticosteroid to affected areas and give a nonsedating second-generation oral antihistamine (such as cetirizine) to the subjects. However, more severe delayed hypersensitivity reactions require a thorough medical evaluation and may necessitate hospitalization and treatment with systemic steroids.
Source: (Khan et al. 2022)	

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Appendix S Protocol History

Date	Amendment Number	Amendment Type	Region
19 July 2024	Amendment 3	Substantial	Global
09 November 2023	Amendment 2	Substantial	Global
02 December 2021	Amendment 1	Substantial	Global
11 June 2020	Initial version	Not Applicable	Global

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

- Clarify the gliadin strength in TAK-101.
- Exclude subjects with known hypersensitivity reaction and/or allergy, including anaphylaxis, to wheat and/or gluten.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	Sections Affected by Change	Description of Each Change and Rationale	
	Location	*Description*	*Rationale*
1.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 8.1.3 Dose and Regimen	Updated group names for cohort 1 and cohort 2.	Clarification.
2.	Section 2.0 STUDY SUMMARY	Updated number of sites and deleted specific country names.	To include number of sites globally.
3.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	Deleted the secondary objective on dose response relationship of TAK-101.	Clarification.
4.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added an exclusion criteria to exclude subjects with other inflammatory GI disorders or systemic autoimmune diseases.	Clarification.
		Updated an exclusion criteria to exclude known allergic reactions ie, preexisting wheat allergy, hypersensitivity, and/or anaphylaxis including wheat-dependent-exercise induced anaphylaxis	

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		(WDEIA).	
5.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added the requirement for evaluation by allergist with concern for subjects with possible history of urticaria, angioedema, or anaphylaxis to wheat.	To include the requirement for allergist evaluation for patients with suspected allergy.
6.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Updated the exclusion criteria to exclude subjects who had COVID-19 with ongoing symptoms or evidence of infection instead "within past 2 months".	To broaden the selection criteria given current endemic COVID-19.
7.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added a separate exclusion criteria on allergy and/or intolerance to TAK-101 or any of its ingredients or excipients.	To exclude subjects with known allergy to TAK-101.
8.	Section 4.1.2 Name and Description of Study Drug	Updated the strength of gliadin extract drug substance in TAK-101.	To keep TAK-101 nomenclature consistent with other regulatory documents.
9.	Section 4.1.2 Name and Description of Study Drug	Added antigen presenting cells in TAK-101 mechanism of action.	Clarification.
10.	Section 4.1.3 Summary of Nonclinical Findings	Added clarifying information. Added text for the HLA-DQ8/HuCD4 transgenic mouse model (TGLIA-1.005). Updated study numbers in text and Table 4.a. Added a sub section (Section 4.1.3.2.3) on "Reproductive Toxicity".	Consistency with IB edition 4.
11.	Section 4.1.3 Summary of Nonclinical Findings Section 16.0 REFERENCES	Added a new reference Freitag et al. 2020.	Clarification.
12.	Section 4.1.4 Summary of Clinical Findings	Added the reason to make changes in dose administration.	Clarification.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		Added the incidences of moderate infusion reactions and Grade 1 elevations in liver enzymes.	
13.	Section 4.1.4 Summary of Clinical Findings Section 16.0 REFERENCES	Added a new reference for the information that IRRs were felt to be consistent with nanoparticle effects.	To differentiate from potential IgE mediated reactions.
14.	Section 4.3 Benefit/Risk Profile Section 4.3.1 Risk Related to Oral Gluten Exposure	Added the risk of including patients with wheat allergy.	Clarification.
15.	Section 4.3 Benefit/Risk Profile	Added the clarification on liver function tests to understand when to administer 2nd dose of study drug. Added the severity of reported TEAEs.	Clarification.
16.	Section 4.3.1 Risk Related to Oral Gluten Exposure	Added the names of gastrointestinal symptoms and neurological/neurocognitive manifestation symptom.	Clarification.
17.	Section 5.1.3 Exploratory Objectives	[redacted].	Clarification.
18.	Section 6.1 Study Design	Added Table 6.a on detailed dose and regimen. Updated the study design schematic (Fig 6.a). Added the study schematic for dose cohorts (Fig 6.b).	Consistency with updated IB edition 4.
19.	Section 6.1 Study Design Section 8.1.3 Dose and Regimen Section 13.2 Interim Analysis and Criteria for Early Termination	Updated the criteria for interim analysis.	Clarification.
20.	Section 6.3.1	Updated additional TEAEs, CTCAE Grade 3 or Grade ≥ 4 AEs, anaphylaxis/hypersensitivity allergic reactions as reasons to pause enrollment.	Clarification.
21.	Section 7.1 Inclusion Criteria	Updated the BMI in criteria #7.	To broaden inclusion criteria and support study diversity

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
			measures.
22.	Section 7.1 Inclusion Criteria Section 9.1.9.1 Male Subjects and Their Female Partners Section 9.1.9.2 Female Subjects and Their Male Partners Section 9.1.10 Pregnancy	Updated the number of days after last dose to continue using contraception for male and female subjects.	To broaden inclusion criteria and support study diversity measures.
23.	Section 7.2 Exclusion Criteria	Added the number of half-lives in exclusion criteria #1. Updated the number of days after last dose for positive pregnancy test for female subjects in criteria #11. Updated the number of days after last dose for sperm donation for male subjects in criteria #12. Added the current diagnosis of malignancy. Removed the type of abuse from criteria #13.	To update the exclusion criteria.
24.	Section 7.3 Excluded Medications	Added the time frame for excluded medications.	Clarification.
25.	Section 7.4 Diet, Fluid, Activity Control and Treatment Facilities	Added the reference to the Pharmacy Manual. Removed the definition of "gluten-free".	Clarification.
26.	Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling	Changed the location of "management of IRRs" from Section 8.1.1.3 to Section 10.5.1.1.	Clarification.
27.	Section 8.1.1.3 Rescue Medications	Added sympathomimetic agonists epinephrine as a rescue medication.	Clarification.
28.	Section 8.1.3 Dose and Regimen	Updated total infusion time. Updated the Table 8.a with dose grouping. Added the information on avoidance of exercise	Clarification.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		before or after the infusion.	
29.	Section 9.1 Study Procedures	Added a subsection 9.1.18 on definitions of end of study and end of treatment.	Clarification.
30.	Section 9.1.6 Documentation of Concomitant Medications	Added rescue medications to be recorded in the eCRF.	Clarification.
31.	Section 9.1.9.3 Definitions and Procedures for Contraception and Pregnancy Avoidance Table 9.b Acceptable Contraception Methods and Lactation Guidance for This Study	Updated additional methods for contraception and pregnancy avoidance. Added clarification on sexual abstinence. The list of acceptable methods of contraception was revised into tabular format (9.b and 9.c).	Clarification.
32.	Section 9.1.12 Biomarker Collection	Deleted blood sample for HLA typing, and sample collection column, and replaced PK with ADA for specimen #7, in Table 9.d and the subsection for the same. Deleted subsection 9.1.12.3 Blood sample for HLA typing.	Clarification.
33.	Section 9.1.12.2 Blood Sample (Whole Blood) for Immunophenotyping and Stimulation	Added the details about ex-vivo IL-2 assay.	Clarification.
34.	Section 9.1.12.4 Plasma Sample for Protein	Added the details about additional plasma biomarkers.	Clarification.
35.	Section 9.1.12.5 Urine Sample for Gluten	Added the details about urine sample collection.	Clarification.
36.	Section 9.1.13.1 Collection of Plasma for PK Sampling	Added the method of PK sample assay.	Clarification.
37.	Section 9.1.14.1 Serum Sample for Immunogenicity	[redacted]	Clarification.
38.	Section 9.2 Gluten Exposure Compliance	Updated the details on date and time of gluten consumption and urine	Clarification.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		sample assessment.	
39.	Section 10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS	Added Section 10.4 on AESIs and potential risks with TAK-101 treatment.	Clarification.
40.	Section 10.1.3 Additional Points to Consider for PTEs and AEs	Deleted the point on anticipated AEs.	To avoid duplication with AEs related to gluten exposure.
41.	Section 10.1.3 Additional Points to Consider for PTEs and AEs	Added each use of rescue medication as an AE.	Clarification.
42.	Section 10.1.4 SAEs	Deleted COVID-19 pneumonia and related disease from Table 10.a.	To exclude COVID-19 from the significant AE list.
43.	Section 10.1.5 AESIs	Deleted hepatotoxicity, IRRs, thrombosis, and decreased platelet count.	Clarification.
44.	Section 10.2.1.1 PTE and AE Collection Period	Added the time frame for routine collection of AEs.	Clarification.
45.	Section 10.2.1.3 AESIs	Deleted additional risk mitigation including mixing of IV infusion bag.	Clarification.
46.	Section10.5.1.1 IRR	Added the details on the onset timing of IRRs after infusion. Replaced “moderate or worsening” with “clinically significant”.	Clarification.
47.	Section 10.5.2.1 Hepatotoxicity (Reversible liver injury)	Added the exclusion of subjects with clinically significant liver disease or ALT/AST/Total bilirubin >1.5x ULN. Added the timepoints for LFT tests. Added the reference to Appendix E for additional monitoring information.	Clarification.
48.	Section 10.5.2.2 Thrombosis	Added the details on TAK-101-related pulmonary thrombosis with mortality from a single rat toxicity study.	Clarification.
49.	Section 10.5.2 Important Potential	Added subsection 10.5.2.3	To include all potential risks.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Risks	on allergic reactions in patients with preexisting wheat allergy, hypersensitivity, and anaphylaxis including WDEIA.	
50.	Section 11.1 IDMC	Replaced the text in this section to include only relevant information.	Clarification.
51.	Section 13.1 Statistical and Analytical Plans	Added Section 13.1.7 on immunogenicity analysis.	To include data on immunogenicity analysis.
52.	Section 14.1 Study-Site Monitoring Visits	Added language for remote monitoring visits.	Clarification.
53.	Section 14.3 Quality Assurance Audits and Regulatory Agency Inspections	Deleted the individual agency names.	Clarification.
54.	Appendix A Schedule of Study Procedures	Table A-1: Deleted Visit 10.a for PTE/AE assessment. Added additional tests including compliment, tryptase, and histamine under clinical lab tests. Added Visit 10.a for urinalysis. [redacted] Deleted follow up telephone call.	Clarification.
55.	Appendix A Schedule of Study Procedures	Table A-2: updated footnote for urine sample assessment.	Clarification.
56.	Appendix I, Appendix J, Appendix K, Appendix L	Additional appendices were included to support the protocol data.	Clarification.

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Protocol Amendment 1 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

Add a third dose of TAK-101 after the Week 20 gluten challenge.

Exclude subjects with a history of thromboembolic events from participating in the study.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Section 6.1 Study Design Section 8.1.3 Dose and Regimen Section 8.2 Study Drug Assignment and Dispensing Procedures Section 9.1.4 Vital Sign Procedure Section 9.1.13.1 Collection of Plasma for PK Sampling Section 9.1.15.3 [redacted] Appendix A Schedule of Study Procedures	Added a third dose of TAK-101 treatment after the Week 20 final gluten challenge for all randomized subjects.	To enable collection of clinical data on a third dose of TAK-101 and to offer TAK-101 treatment to subjects who were randomly assigned to receive placebo.
2.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives Section 5.2.2 Secondary Endpoints	Added dose regimen to the safety and immunogenicity secondary objectives for various dose levels.	To include the different TAK-101 dosing regimens in the dosing and immunogenicity secondary objectives.
3.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	[redacted]	[redacted]
4.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	Revised the secondary objective for characterization of TAK-101 pharmacokinetics (PK) to measurement of TAK-101 plasma concentration.	To clarify that a full PK profile is not the objective.
5.	Section 2.0 STUDY SUMMARY Section 4.1.5 Summary of Clinical Findings Section 8.1.3 Dose and Regimen	Revised estimation of infusion time and volume per time increment.	To allow for an infusion rate that increases gradually over the duration of the infusion rather than a constant, higher infusion rate.
6.	Section 2.0 STUDY SUMMARY	Added that the safety and laboratory data from the	Clarification.

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Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Section 8.1.3 Dose and Regimen	third infusions given to the first 5 subjects will be reviewed by independent data monitoring committee (IDMC) and, if needed, recommended changes based on these observations.	
7.	Section 2.0 STUDY SUMMARY Appendix A Schedule of Study Procedures	Extended duration of study treatment and period of evaluation.	To account for extra time needed for the third dosing.
8.	Section 2.0 STUDY SUMMARY Section 5.2.1 Primary Objective Section 5.2.1 Primary Endpoint Section 4.2 Rationale for the Proposed Study Section 9.1.5 Primary Efficacy Measurement	Specified that the primary endpoint is specific to HLA-DQ2 positive subjects.	To refine the primary endpoint for subjects who are HLA-DQ2 positive.
9.	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Section 13.1.3 Efficacy Analysis	Revised secondary endpoints for change in Celiac Disease Symptom Diary Version 2.1 (CDSD v2.1; 24-Hour Recall) 3-day average score and 3-day peak score.	To specifically assess nausea severity and to clarify the definitions and calculations of the endpoints for consistency throughout the protocol.
11.	Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis	Added that if the model does not converge, additional covariance structure will be used in the order specified in the statistical analysis plan.	Clarification.
12.	Section 4.1.2 Name and Description of Study Drug	Changed liquid for reconstitution of TAK-101 from sterile water to 200 mL 0.9% sterile saline.	Correction.
13.	Section 4.1.2 Name and Description of Study Drug	Added additional information on the mechanism of action of TAK-101.	Clarification.
14.	Section 4.1.3.2 Nonclinical Safety Findings	Summarized the results from relevant nonclinical safety studies in rats and	To provide nonclinical evidence to describe the unexpected nonclinical

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Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		monkeys.	safety finding of thrombosis in rats and to support the addition of a TAK-101 third dose after the Week 20 gluten challenge.
15.	Section 4.1.4Summary of Clinical Findings	Included reduction of epithelial-interacting [redacted] T cells in additional supportive data for efficacy of TAK-101. Added that all infusion-related reaction (IRR) events resolved with or without medical intervention and without sequelae.	To add specificity to the supportive data.
16.	Section 4.3 Benefit/Risk Profile	Replaced the potential risk of thrombocytopenia with important potential risks of thrombosis and hepatotoxicity, identified risk of IRR, and the potential risk of decreased platelet count.	To incorporate the potential risk of thrombosis based on an unexpected nonclinical safety finding in rats.
17.	Section 4.3 Benefit/Risk Profile Section 7.5 Criteria for Discontinuation of Study Drug Appendix A Schedule of Study Procedures Appendix E Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up	Revised timing for, and parameters of, liver tests for second dose eligibility to remain within 2× the upper limit of normal (ULN).	To account for small fluctuations in liver tests unrelated to study procedures.
18.	Section 4.3.1 Risk Related to Oral Gluten Exposure	Added rationale for including the run-in gluten challenge in the study design.	Clarification.
19.	Section 5.1.3 Exploratory Objectives Section 5.2.3 Exploratory Endpoints Section 9.1.12.1 Blood Sample (PBMC) for Tetramer Staining and ELISpot	[redacted]	[redacted]

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Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
20.	Section 5.2.3 Exploratory Endpoints Section 9.1.15.3 [redacted] Section 10.2.1.2 PTE and AE Reporting Section 13.1.3 Efficacy Analysis Appendix A Schedule of Study Procedures	[redacted]	Correction.
21.	Section 5.2.3 Exploratory Endpoints	[redacted]	[redacted]
22.	Section 5.2.3 Exploratory Endpoints	[redacted]	[redacted]
23.	Section 6.3.1	Updated the circumstances that may warrant termination of the study.	Clarification.
24.	Section 6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)	Added the criteria for premature study termination or suspension based on any significant violation of GCP.	Clarification.
25.	Section 7.1 Inclusion Criteria	Updated note in inclusion criterion #1 for participation parameters in subjects who have intermittent celiac disease symptoms.	To include details for assessment of eligibility in subjects who have intermittent CeD symptoms.
26.	Section 7.2 Exclusion Criteria	Specified that subjects cannot receive other investigational compounds during the study (exclusion criterion #1).	Clarification.
27.	Section 7.2 Exclusion Criteria Section 2.0 STUDY SUMMARY	Added an exclusion criterion (#18) to exclude	To exclude subjects who may be at higher risk of

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Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
		subjects with a history of previous thromboembolic events.	thrombosis, which has been added as a potential risk on the basis of an unexpected nonclinical safety finding in rats.
28.	Section 7.2 Exclusion Criteria Section 2.0 STUDY SUMMARY	Changed the cut off level of ALT, AST, and total bilirubin from >1× the ULN to >1.5× the ULN.	Correction.
29.	Section 7.2 Exclusion Criteria	Added an exclusion criterion (#19) for subjects who have symptoms after the gluten challenge.	To exclude subjects who are unwilling to undergo additional gluten challenges after the first challenge.
30.	Section 7.3 Excluded Medications	Added immunosuppressants and corticosteroids to list of excluded medications.	Clarification.
31.	Section 7.6 Criteria for Withdrawal of a Subject from the Study	Added adverse event (AE) leading to discontinuation as a criterion for study withdrawal.	To increase specificity of reasons for study withdrawal.
32.	Section 7.7 Procedure for Discontinuation or Withdrawal of a Subject	Clarified that subjects who discontinue or are withdrawn after randomization will not be replaced.	Clarification.
33.	Section 8.1.1.4 Challenge Agents	Clarified that gluten will be provided to the subjects by the site.	Clarification.
34.	Section 8.1.3 Dose and Regimen	Removed Group G (1 mg/kg TAK-101 followed by placebo) from Table 8.a.	Correction.
35.	Section 8.1.3 Dose and Regimen	Added the instructions of dose administration to reduce the risk of adverse events.	Clarification.
36.	Section 8.1.4 Overdose	Added maximum TAK-101 dose being used in the study is 500 mg.	To clarify the definition of overdose.

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37.	Section 8.1.4 Overdose Section 10.1.3 Additional Points to Consider for PTEs and AEs	Changed text to indicate that all cases of overdose are considered AEs and will be documented in the Dosing section of the electronic case report form (eCRF), regardless of whether signs or symptoms accompany the case of overdose.	To clarify the process of documented cases of overdose.
38.	Section 9.1.4 Vital Sign Procedure Appendix A Schedule of Study Procedures	Clarified that weight and height measurements are collected at screening and before the third infusion.	Clarification.
39.	Section 9.1.8 Procedures for Clinical Laboratory Samples Appendix A Schedule of Study Procedures	Added glycosylated hemoglobin to screening laboratory tests.	To verify that glycosylated hemoglobin is <8% in subjects with type 1 diabetes.
40.	Section 9.1.8 Procedures for Clinical Laboratory Samples Appendix A Schedule of Study Procedures	Included D-dimers, prothrombin fragment F1+2, and thrombin-antithrombin complex to coagulation assessments at Visits 3.a, 4.a, and 10.a.	To increase specificity of instructions for assessment of coagulation parameters and assess changes in parameters relevant to thrombosis, in light of the unexpected nonclinical safety finding of thrombosis in rats.
41.	Section 9.1.8 Procedures for Clinical Laboratory Samples	Included sample for CRS to screening laboratory tests.	To make it consistent with schedule of study procedures.
42.	Section 9.1.10 Pregnancy	Specified that all pregnancies in enrolled subjects or in female partners of male subjects will be followed for pregnancy outcome. Deleted that pregnancies will remain blinded to the study team.	Clarification.
43.	Section 9.1.12 Biomarker Collection Section 9.1.12.1 Blood Sample (PBMC) for Tetramer Staining and ELISpot Section 9.1.12.2 Blood Sample (Whole Blood) for Immunophenotyping and	Added an additional biomarker using whole blood for immunophenotyping and ex vivo stimulation at	To specify sampling of whole blood for immunophenotyping and stimulation before and after the 6-day gluten

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	Stimulation Appendix A Schedule of Study Procedures	Visits 3, 5, and 6.	challenge.
44.	Section 9.1.12.1 Blood Sample (PBMC) for Tetramer Staining and ELISpot	Added text explaining that the enzyme-linked immunospot (ELISpot) and Tetramer assays will only detect T-cell responses in subjects who are HLA-DQ2 positive.	Clarification.
45.	Section 9.1.12.1 Blood Sample (PBMC) for Tetramer Staining and ELISpot	Corrected "HLA-DQ2.5" to "HLA-DQ2".	Correction.
46.	Section 9.1.15.1 CDSD v2.1 and supplementary questions (24-Hour [redacted]) Section 9.1.15.2 [redacted]	[redacted]	Clarification.
47.	Section 9.1.15.4 Additional Exploratory Questions	[redacted]	Clarification.
48.	Section 10.1.5 AESIs	Added thrombosis, hepatotoxicity, and decreased platelet count to the list of AEs of special interest for this study.	To enable to assessment of events of thrombosis, which is now considered a potential risk based on an unexpected nonclinical safety finding in rats.
49.	Section 10.1.6 Intensity of PTEs and AEs Appendix G DILI Severity Grading Scales	Added new appendix providing a severity scale for drug-induced liver injury.	Clarification.
50.	Section 10.2.1.1 PTE and AE Collection Period	Revised the end of the AE collection period to Visit 10.a (Week 24).	Clarification.
51.	Section 10.4 AESIs and Potential Risks with TAK-101 Treatment	Added the section.	To create a section for risk mitigation and AESI management.
52.	Appendix A Schedule of Study Procedures	Added option for coronavirus disease 2019 (COVID-19) testing under medical history according	To allow for COVID-19 testing as applicable.

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		to site guidance and/or at the discretion of the investigator.	
53.	Appendix A Schedule of Study Procedures	Removed collection of medication history at all visits except the Week -6 screening visit.	Correction.
54.	Appendix A Schedule of Study Procedures	Removed physical examination for Visits 7-9.	Correction.
55.	Appendix A Schedule of Study Procedures	Removed duplicate row for randomization.	Correction.
56.	Appendix A Schedule of Study Procedures	Added Visit 10, at which infusion of a third dose is performed, and a follow-up telephone call 2 to 4 weeks afterward.	To assess safety and tolerability of a third dose of TAK-101.
57.	Appendix A Schedule of Study Procedures	Added that clinical laboratory tests will be conducted before and after dosing on infusion days to footnote d.	Clarification.
58.	Appendix A Schedule of Study Procedures	Added Visit 10.a for liver and coagulation tests only (after study treatment infusion at Visit 10).	To provide for assessment of liver enzymes and coagulation status following infusion of study treatment.
59.	Appendix A Schedule of Study Procedures	Added Visits 3.a, 4.a, and 10.a to footnote a.	To allow for the possibility of these study visits to occur in the clinic or at home as deemed feasible by the sponsor/site.
60.	Appendix A Schedule of Study Procedures	Clarified that liver enzymes/bilirubin must be collected before dosing on Day 8/Visit 4, must be analyzed by the central laboratory regardless of collection site, and must be confirmed to be ≤2 × ULN before the second dose is administered at Visit 4.	Clarification.

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61.	Appendix A Schedule of Study Procedures	Specified that tetramer staining and ELISpot at Visit 5 use peripheral blood mononuclear cells.	Clarification.
62.	Appendix A Schedule of Study Procedures	Included RNA in plasma protein sampling.	To add a plasma sample for RNA assessment.
63.	Appendix A Schedule of Study Procedures	[redacted]	Clarification, correction, and to give a more efficient presentation in assessment schedule.
64.	Appendix A Schedule of Study Procedures	Removed sampling for complement from the early termination visit.	Correction.
65.	Appendix A Schedule of Study Procedures	Sampling for cytokine release syndrome removed from Visit 5.	Correction.
66.	Appendix A Schedule of Study Procedures	Added assessment with CDSD v2.1 (24-Hour Recall) to Visit 1 (screening/run-in)	To obtain baseline assessment.
67.	Appendix A Schedule of Study Procedures	Combined specification for [redacted].	Simplification of assessment schedule.
68.	Appendix H Definition of IRRs, Allergic Reaction, and Anaphylaxis	Added the definitions that were missing in the protocol.	Clarification.
69.	Appendix F CDSD Version 2.1 (24-Hour Recall) Appendix G [redacted] Appendix H [redacted] Appendix I [redacted] Appendix J [redacted]	Removed appendices containing patient-reported outcome instruments from the protocol.	To avoid duplication with other study documents.

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	Appendix K Additional Exploratory Questions		

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Signature Page for TAK-101-2001 Protocol Amend 3 2024-07-19

Title: Amend 2 to A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose R

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