Clinical Study Protocol

NCT Number: NCT05353985

Title: A Phase 2, Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of TAK-062 for the Treatment of Active Celiac Disease in Subjects Attempting a Gluten-Free Diet

Study Number: TAK-062-2001

Document Version and Date: Amendment no. 5, 16 November 2023

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.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of TAK-062 for the Treatment of Active Celiac Disease in Subjects Attempting a Gluten-Free Diet

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421, USA		
Study Number:	TAK-062-2001		
IND Number:	137372	**EudraCT Number:**	2020-005438-14
Compound:	TAK-062		
Date:	16 November 2023	**Amendment Number:**	5

Amendment History:

Date	Amendment Number	Amendment Type	Region
16 November 2023	5	Substantial	Global
02 June 2023	4	Substantial (not submitted to European Health Authorities)	Global
26 October 2022	3	Substantial	Global
22 July 2022	2	Substantial	Global
23 June 2022	1	Substantial	Global
18 January 2022	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center 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	United States, Canada, and the Rest of the World
Serious adverse event and pregnancy reporting	Fax: +1-224-554-1052 Email: PVSafetyAmericas@tpna.com
Medical Monitor (medical advice on protocol and study drug)	[redacted], Clinical Science
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted], Clinical Science

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): 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.

[redacted], MD, MS [redacted], Clinical Science	Date
[redacted], PhD [redacted], Statistical and Quantitative Sciences	Date

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the investigator (Appendix C).
- I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix E of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 5 Summary of Changes

Protocol Amendment 5 Summary and Rationale:

This document describes the changes to the protocol incorporating Amendment 5. The primary reason for this amendment is to update approximate subject numbers per cohort and treatment arms and to clarify combining of placebo groups of Cohort 1 and Cohort 2 for analyses, exclusion criteria, strategies for reduction of potential protocol deviations, handling of intercurrent events, and withdrawal-from-treatment criteria.

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 5			
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 9.3.6.1 CDSD v2.1 Table 13.a [redacted] Appendix A Schedule of Study Procedures	Clarified that Version 2.1 of the Celiac Disease Symptom Diary (CDSD) will be used.	Clarification.
2.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.a Schematic of Study Design Table 8.b Dose and Regimen Section 13.3 Determination of Sample Size	Updated the planned approximate sample size from 377 to 357 to account for the combining of subjects within the placebo gluten-containing simulated inadvertent gluten exposure (SIGE) arms from Cohorts 1 and 2 for analysis. Updated the approximate number of subjects to be enrolled in Cohort 2 from 257 to 237. Updated the approximate number of subjects to be enrolled to Cohort 2 Group 1 (TAK-062 placebo [redacted] + SIGE bar [redacted] from 50 to 30. Added the number of adults and adolescent subjects per cohort.	Update. There will be no pause between the end of Cohort 1 enrollment and the beginning of Cohort 2 enrollment, and no difference is expected for the 2 placebo-SIGE arms under the same eligibility criteria. For these reasons, the decision was made to reduce the size of the placebo gluten-containing SIGE arm in Cohort 2 from 50 to 30 subjects, as all subjects from the Cohort 1 placebo gluten-containing SIGE arm will be combined with the placebo gluten-containing SIGE arm from Cohort 2 in the analyses.

Protocol Amendment 5			
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***
3.	Section 2.0 STUDY SUMMARY Section 4.1 Background Section 6.1 Study Design Section 6.2.1 Rationale for Study Design Section 13.1.1 Analysis Sets Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12 Section 13.3 Determination of Sample Size	Updated wording for inadvertent gluten exposure (ie, SIGE) to "gluten-containing SIGE."	Clarification of terminology.
4.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Clarified wording for when subjects will receive simulated SIGE bars with or without gluten [redacted]	Clarification.
5.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Clarified the process for inclusion of subjects older than 75 years, which will require discussion with the medical monitor.	Clarification.
6.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Clarified wording of gluten-free SIGE bars [redacted] and [redacted] from Week -2 to Day -1.	Correction.
7.	Section 2.0 STUDY SUMMARY	Added clarification that subjects will be excluded upon development of symptoms that suggest a confounding nongluten food intolerance.	Clarification.

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8.	Section 2.0 STUDY SUMMARY Section 5.2.1 Primary Endpoint Section 5.2.4 Exploratory/Additional Endpoints Section 6.2.3.1 Efficacy Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	Updated wording for the primary endpoint from change in once-per-week average CDSD gastrointestinal (GI) symptom severity to change in "weekly CDSD GI symptom severity score" to clarify main criteria for evaluation and updated primary estimand attributes and text. Updated phrasing from "once per week" to "weekly" for consistency in discussing the primary endpoint.	Clarification.
9.	Section 2.0 STUDY SUMMARY Appendix A Schedule of Study Procedures	Updated the number of subjects in the subset to receive second [redacted] before SIGE for a test/retest assessment from approximately 30 to approximately 40.	Correction.
10.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 6.2.3.4 Urine-Based Biomarker: GIP Appendix A Schedule of Study Procedures	Added clarification that missed gluten immunogenic peptide (GIP) samples will not be considered a protocol deviation.	Clarification of expectations.
11.	Section 2.0 STUDY SUMMARY Section 7.4 Rescue Medications Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	Clarified that rescue medications will be administered only for symptoms considered related to celiac disease (CeD).	Clarification.
12.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 7.1 Inclusion Criteria	Clarified that adolescent subjects will be enrolled into Cohort 2 only after review by the independent data monitoring committee (IDMC) at interim analysis (IA).	Clarification.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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13.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Updated exclusion criteria text to allow subjects with systemic autoimmune disease who do not have GI symptoms and are stable and to allow subjects with proton pump inhibitor–responsive eosinophilic esophagitis to be discussed with the study medical monitor to determine eligibility.	Update.
14.	Section 9.3.7.4 Research Subject Responsibilities Training	Clarified that subjects may receive training once training is available.	Clarification.
15.	Section 2.0 STUDY SUMMARY Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	[redacted]	[redacted]
16.	Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Added sample-size reevaluation for power and dropout rate for the combined placebo groups in Cohort 1 and Cohort 2. Clarified that higher analytical power should be expected due to the combining of placebo subject groups.	Addition of sample-size reevaluation for the combining of placebo cohorts.
17.	Section 4.1 Background Section 6.2.1 Rationale for Study Design	Updated instances of "without SIGE" to "gluten-free SIGE" for consistency across all sections.	Clarification.
18.	Section 4.1 Background	Removed "and regulatory authority feedback has been incorporated" from the description of CDSD and clarified that patient-reported outcomes "may" (changed from "will") enable CDSD to be used as a primary endpoint.	Clarification.
19.	Section 6.1 Study Design	Clarified that on-study gluten intake will be assessed by measuring GIP in urine.	Clarification.

Protocol Amendment 5			
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20.	Section 6.1 Study Design	Corrected improvement in PGIS (Patient Global Impression of Severity) during [redacted] run-in period from "Week -2 through Day 0" to "Week -2 to Day -1."	Correction.
21.	Section 6.1 Study Design Section 6.2.3.2 Tissue-Based Biomarkers: Vh:Cd and IELs Section 9.3.12.2 Biomarker Collection Appendix A Schedule of Study Procedures	Added clarification that predose plasma and serum collections for exploratory analysis will be performed at the same visits as pharmacokinetic (PK) collection.	Clarification of timing of biomarker collection to minimize confusion with PK collections.
22.	Figure 6.a Schematic of Study Design	Updated presentation of the duration of treatment for Week 12 and Week 24 for clarity. Added [redacted] test/retest subset. Updated "Gluten-containing SIGE" and "Gluten-Free SIGE" for consistency with body text.	Clarification.
23.	Section 6.2.1 Rationale for Study Design	Updated wording to clarify that adult subjects in Cohort 2 will receive gluten-containing or gluten-free SIGE bars.	Clarification.
24.	Section 6.2.2 Rationale for Dose Section 7.6 Criteria for Discontinuation or Withdrawal of a Subject	Clarified that a break in gluten-containing SIGE bars due to worsened CeD symptoms for more than 2 weeks will result in a subject's withdrawal from treatment, but the subject will remain in the study for safety monitoring.	Clarification.
25.	Section 6.2.3.1 Efficacy	Added that the CDSD is not yet validated "for the intended context of use."	Clarification of regulatory language.
26.	Section 6.2.3.2 Tissue-Based Biomarkers: Vh:Cd and IELs Appendix A Schedule of Study Procedures	Updated subheading to "Other Exploratory Biomarkers." Added examples of exploratory biomarkers from plasma and serum collections for improved noninvasive patient selection or disease monitoring.	Correction.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
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27.	Section 7.1 Inclusion Criteria	Corrected the upper age limit for adolescents in criterion 10.	Correction.
28.	Section 7.2 Exclusion Criteria Section 7.3 Excluded Medications	Updated reporting for prior and concomitant medication from "6 months" to "90 days" for consistency throughout the protocol.	Clarification.
29.	Section 7.2 Exclusion Criteria	Added "eg," to the list of food allergies in criterion 18 to indicate nonexhaustive examples. Added criterion 29 to exclude subjects with active malignancy or malignancies diagnosed within 5 years prior to screening. Subjects with Stage 0 or nonrecurrent Stage 1 disease will not be excluded.	Clarification of eligibility criteria.
30.	Section 9.3.6 PRO Assessments Section 9.3.6.1 CDSD v2.1 Section 13.1.3.3 Other Efficacy Endpoint Analyses Appendix A Schedule of Study Procedures	Clarified that the CDSD and supplementary frequency questionnaire are separate measures competed at the same time points. Updated the text to describe CDSD from a "8-item" to "5-item" questionnaire to clarify that CDSD is a separate measure from the frequency of CeD symptoms, which is captured by the supplemental frequency questionnaire.	Clarification of 2 different measures used for symptom severity and symptom frequency.
31.	Section 9.3.9 Endoscopy and Biopsy Collection	Removed a statement that subjects, site staff, and study team members will remain blinded to postrandomization histopathological findings throughout the study.	Correction to align with blinding procedures.
32.	Section 13.1.3 Efficacy Analysis	Clarified that full analysis set–SIGE analysis will include all subjects randomized to receive placebo [redacted] and gluten-containing SIGE bars [redacted] from Cohorts 1 and 2.	Update to align with the combining of placebo groups from Cohorts 1 and 2.

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33.	Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	Updated the definition of AUC from "area under the concentration-time curve" to "area under the curve." Clarified estimands using AUC from Day 1 to Week 12 for GI severity will use daily scores. Clarified that severity scores range from 0 (no symptoms) to 4 (very severe).	Clarification.
34.	Section 13.1.3.2 Secondary Efficacy Endpoint Analysis	Included "other reasons for discontinuations" that are not otherwise listed.	Correction.
35.	Section 13.2 IA and Criteria for Early Termination Table 13.a [redacted]	[redacted]	[redacted]
36.	Appendix A Schedule of Study Procedures	Added "Section" to clarify a link to the text for pregnancy testing (in Footnote g).	Clarification.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-062	
Title of Protocol: A Phase 2, Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of TAK-062 for the Treatment of Active Celiac Disease in Subjects Attempting a Gluten-Free Diet	**IND No.:** 137372	**EudraCT No.:** 2020-005438-14
Study Number: TAK-062-2001	**Phase:** 2	

Study Design:

Despite attempts to maintain a gluten-free diet (GFD), many individuals with celiac disease (CeD) continue to have symptoms and/or intestinal damage due to inadvertent gluten exposure. TAK-062 is a computationally designed enzyme intended to reduce or prevent symptoms and intestinal damage related to gluten exposure. This is a 2-cohort phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of TAK-062 for treatment of ongoing symptoms and small intestinal mucosal injury due to gluten exposure in subjects with CeD attempting to maintain a GFD. In addition, this study is designed to further evaluate the psychometric properties of the Celiac Disease Symptom Diary (CDSD) Version (v)2.1, [redacted], and to provide data on the optimal histologic measure for assessment of response to treatment in CeD.

Approximately 357 subjects with CeD and both ongoing symptoms and small intestine villous atrophy on duodenal biopsy, despite attempting to maintain a GFD for at least 12 months, will be enrolled and randomly assigned into 1 of 2 treatment groups in the Cohort 1 proof of concept study and 1 of 6 treatment groups in the Cohort 2 dose-ranging study (see the Number of Subjects section below):

The interim analysis (IA) will be initiated when at least 75% of the subjects in Cohort 1 have either completed 12 weeks of treatment or have dropped out to determine inclusion of adolescents in Cohort 2. Cohort 1 data will be reviewed by an external independent data monitoring committee (IDMC) and shared with health authorities and independent ethics committees (IECs)/institutional review boards (IRBs) as required by region, before enrollment of adolescents in Cohort 2. If efficacy and safety data from Cohort 1 is considered acceptable, Cohort 2 will also include adolescents aged 12 to 17 years. Adolescents will receive only gluten-free simulated inadvertent gluten exposure (SIGE) bars.

This study will consist of 4 periods in each cohort: a 2- to 4-week screening period (Week -8 to Week -4), a 4-week single-blind placebo run-in (Week -4 to Day -1), a 24-week double-blind treatment period (Week 0 to Week 24), and a 4-week safety follow-up period. At the first visit (Week -8), subjects will consume 1 gluten-free SIGE bar to ensure no intolerance to any of the nongluten components of the bar. During the screening period (between Week -8 visit to Week -4 visit), subjects will complete the CDSD daily to confirm they have at least 1 ongoing CeD-related gastrointestinal (GI) symptom of moderate or greater severity on at least 3 days out of any consecutive 7-day period. The CeD-related symptom(s) may vary day by day as long as the severity of at least 1 symptom is moderate or greater. Eligible subjects will undergo an esophagogastroduodenoscopy (EGD) with duodenal biopsy [redacted]. In addition, a subset of approximately 40 subjects in total will have a [redacted] and before SIGE for a test/re-test assessment. During the screening period, urine samples will be collected once per week for gluten immunogenic peptide (GIP) to assess systemic exposure to gluten.

During the single-blind run-in period (Week -4 through Day -1), subjects will receive TAK-062 placebo [redacted]

[redacted]. Beginning Week -8, urine samples (first morning void) will be collected once per week for GIP throughout the study. [redacted] While all efforts should be made to obtain weekly urine samples, missed urine GIP samples will not be considered a protocol deviation.

Eligible subjects with villous atrophy on duodenal biopsy (defined as villous height–to–crypt depth ratio [Vh:Cd] <2.5 by central pathology assessment) will be randomly assigned to 1 of 2 treatment groups in Cohort 1 or 1 of 6 treatment groups in Cohort 2 to receive double-blind treatment and gluten-containing SIGE or gluten-free SIGE (Cohort 2) for 24 weeks (Day 1 through Week 24). Initially, all subjects who meet symptom criteria and histologic criteria will be randomized. If more than 10% of planned enrollment in a cohort report a greater than 1 point improvement in Patient Global Impression of Severity during [redacted] run-in period (Week -2 through Day -1), further subjects showing this degree of improvement will be excluded from the cohort.

Randomization will be stratified by celiac serologic status at Visit 1, defined as normal or elevated celiac serology (1 or more of the following: IgA-tissue transglutaminase (tTg) >1 time the upper limit of normal [ULN], IgA–deaminated gliadin peptide [DGP] >2 × ULN, or IgG-DGP >2 × ULN), mild to moderate (Vh:Cd 1.5 to <2.5) versus moderate to severe (Vh:Cd <1.5) histologic injury at baseline, and by use of proton pump inhibitors (PPIs) or histamine type 2 receptor antagonists (yes or no) at Visit 1.

In Cohort 1, all subjects will consume gluten-containing SIGE bars [redacted] with a meal [redacted]
In Cohort 2, adult subjects will receive either gluten-containing or gluten-free SIGE bars with a meal [redacted] throughout the treatment period. [redacted] It is expected that SIGE will result in stable, rather than worsening, symptoms and enteropathy in the TAK-062 placebo groups. If a subject has severe symptoms of diarrhea, nausea, vomiting, or abdominal spasm, that are related to their CeD symptoms, the use of the medications to treat these severe symptoms will be considered as rescue medications.

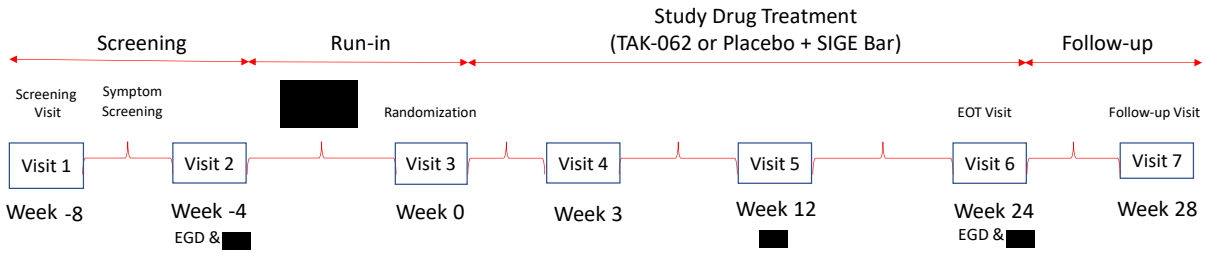
Subjects will report symptoms daily using the CDSD from Week -8 through Week 24.

EGD with biopsy will again be performed at the end of the 24-week treatment period (Week 24). [redacted]

Sparse blood samples to evaluate the pharmacokinetics (PK) of TAK-062 in plasma will be collected in all subjects at Weeks -4, 0, 3, 12, 24, and 28. Approximately 10 adult subjects enrolled in Cohort 1 and 30 adult subjects enrolled in Cohort 2 will participate in the PK subgroup for slightly more intensive collections at Week 0 (randomization) and Week 3 visits.

There is a safety follow-up visit at Week 28, 4 weeks after the last date of treatment.

A diagram of the study design for Cohorts 1 and 2 is located below.



EGD: esophagogastroduodenoscopy; EOT: end of treatment; SIGE: simulated inadvertent gluten exposure; [redacted]

Primary Objective:

The primary objective of this study is:

- To evaluate the efficacy of TAK-062, as measured by the CDSD, for reducing celiac-related symptoms due to gluten exposure in subjects with CeD attempting to maintain a GFD in treated subjects versus placebo controls.

Secondary Objectives:

The secondary objectives of this study are:

- To evaluate the efficacy of TAK-062 for improvement of small intestine mucosal injury due to gluten exposure in subjects with CeD attempting to maintain a GFD in treated subjects versus placebo controls.
- To evaluate the safety and tolerability of TAK-062.

Subject Population: All subjects will be human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 positive, have biopsy-confirmed disease that is clinically active with ongoing GI symptoms as measured by the CDSD and small intestinal villous atrophy on duodenal biopsy, and have been attempting to maintain GFD for ≥12 months. Adolescents and a maximum of 20% of adult subjects without a producible initial biopsy report confirming CeD may be enrolled if they meet the following inclusion criteria:

a) Serology (IgA-tTg) at diagnosis or subsequent visit is at least 2 times the ULN.
b) Histology at screening biopsy at Week -4 must be consistent with Marsh-Oberhuber score of 2 or greater as read by a central pathologist.

Subjects aged 18 and older will be included in Cohort 1. Cohort 1 data will be reviewed by an external IDMC and shared with health authorities and IECs/IRBs as required by region, before enrollment of adolescents in Cohort 2. If data suggests an appropriate benefit-risk profile, Cohort 2 will also include adolescents aged 12 to 17 years, inclusive following IDMC review at IA. Adolescents will receive only gluten-free SIGE bars. Inclusion of subjects older than 75 years of age will require discussion with the study medical monitor prior to enrollment.

Number of Subjects:

Approximate total: 357 randomized subjects

Cohort 1 (120 adults):

1. TAK-062 placebo [redacted] before the start of a meal + gluten-containing SIGE bar with a meal [redacted]: 60 subjects.
2. TAK-062 [redacted] before the start of a meal + gluten-containing SIGE bar with a meal [redacted]: 60 subjects.

Cohort 2 (216 adults and 21 adolescents):

1. TAK-062 placebo [redacted] before the start of a meal + gluten-containing SIGE bar with a meal [redacted]: 30 subjects (adults only).
2. TAK-062 [redacted] before the start of a meal + gluten-containing SIGE bar with a meal [redacted]: 50 subjects (adults only).
3. TAK-062 [redacted] before the start of a meal + gluten-containing SIGE bar with a meal [redacted]: 50 subjects (adults only).
4. TAK-062 placebo [redacted] before the start of a meal + gluten-free SIGE bar with a meal [redacted]: 50 subjects (43 adults, 7 adolescents).
5. TAK-062 [redacted] before the start of a meal + gluten-free SIGE bar with a meal [redacted]: 50 subjects (43 adults, 7 adolescents).

Number of Sites:

Approximate total: 110 sites in the United States, Canada, United Kingdom, and the European Union

6. TAK-062 [redacted] + gluten-free SIGE bar [redacted]: 7 subjects (adolescents only).	
Dose Levels: TAK-062 [redacted]. TAK-062 [redacted]. TAK-062 [redacted]. Placebo [redacted]	**Route of Administration:** TAK-062 tablets orally.
Duration of Treatment: 24 weeks.	**Period of Evaluation:** Approximately 36 weeks.

Main Criteria for Inclusion:

- Biopsy-confirmed CeD.
- Attempting to maintain GFD for at least 12 months as self-reported by the subject.
- Adequate comprehension of a GFD assessed by the site investigator after completion of a knowledge test.
- Small intestinal villous atrophy on duodenal biopsy defined as Vh:Cd <2.5 at Week -4.
- At least 1 CeD-related GI symptom of moderate or greater severity, as measured by the CDSD, on at least 3 days out of any consecutive 7-day period during the screening period (Week -8 visit until Week -4 visit) felt by the investigator to be related to gluten exposure. The CeD-related symptom(s) may vary day by day as long as the severity of at least 1 symptom is moderate or greater. Subjects must meet symptom criteria to undergo EGD/VCE.
- HLA-DQ2 and/or HLA-DQ8 positive.
- For Cohort 1, subjects aged 18 years and older at the time of signing the informed consent form; for Cohort 2, subjects aged 12 years and older, at the time of signing the informed consent form/pediatric assent form. Inclusion of subjects older than 75 years of age will require discussion with the study medical monitor prior to enrollment. Subjects 12 to 17 years of age, inclusive, will only be included in Cohort 2 after IDMC review at the IA.
- Good general state of health according to clinical history and physical examination, in the opinion of the investigator.

Main Criteria for Exclusion:

Subjects with:

1. 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 include systemic autoimmune disease such as scleroderma, psoriatic or rheumatoid arthritis, or lupus that is stable and without GI involvement; well-controlled autoimmune thyroid disease; well-controlled type 1 diabetes; or PPI-responsive eosinophilic esophagitis in symptomatic and histologically confirmed remission.
2. Renal or hepatic disease before randomization based on the following laboratory parameters:
   - Total bilirubin ≥1.5 × ULN unless subject has known Gilbert's syndrome that can explain the elevation of bilirubin, or
   - Serum alanine aminotransferase ≥3 × ULN, or serum aspartate aminotransferase ≥3 × ULN.
   - Glomerular filtration rate (GFR) <49 mL/min. For subjects with GFR 49 to 59 mL/min, inclusion determination should be discussed with the sponsor.

   Note: Subjects may be retested to meet eligibility criteria at the discretion of the investigator.

3. Ongoing systemic immunosuppressant, systemic corticosteroid treatment excluding medication given for endoscopies, or treatment with systemic immunosuppressants or corticosteroids in the 12 weeks before screening.
    - Receiving immunosuppressive doses of corticosteroids: 3 mg per day or more of budesonide for more than 3 consecutive days within 3 months before screening, more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more within 6 months before the first dose, any dose of oral or IV corticosteroids within 30 days of the first dose, or high-dose inhaled corticosteroids (>960 µg/day of beclomethasone dipropionate or equivalent), or other systemic immunosuppressive agents.
4. Ongoing use of over-the-counter digestive enzymes or digestive supplements, other than lactase, including those for gluten digestion. Probiotics are allowable if they were started before screening and not discontinued or changed in dose or type during the study.
5. Ongoing symptoms that are considered by the investigator to be due to other GI conditions, including irritable bowel syndrome, small intestinal bacterial overgrowth, and eosinophilic disorders.
6. Known or suspected type 2 refractory CeD or ulcerative jejunitis.
7. Completed the CDSD on ≤75% of evaluable days during the run-in period until randomization.

Main Criteria for Evaluation and Analyses:

The primary endpoint is:

- Change in weekly CDSD GI symptom severity score from baseline (Week -1) to Week 12.

The secondary endpoints are:

- Change in Vh:Cd from baseline (measured at Week -4) to Week 24.

The safety endpoints are:

- Treatment-emergent adverse events (TEAE), serious adverse events (SAEs), treatment-related TEAEs, electrocardiographic findings (electrocardiogram), vital signs, laboratory parameters, and immunogenicity (posttreatment, positive antidrug antibodies [ADAs] in serum for TAK-062).

Statistical Considerations:

Analysis Sets:

Full analysis set (FAS)–SIGE: All randomized subjects who are randomized to receive gluten-containing SIGE bar.

FAS–no SIGE: All randomized subjects who are randomized to gluten-free SIGE bar.

Safety analysis set (SAF): All randomized subjects who received at least 1 dose of study drug.

SAF–SIGE: All randomized subjects who received at least 1 dose of study drug and gluten-containing SIGE bar.

SAF–no SIGE: All randomized subjects who received at least 1 dose of study drug and gluten-free SIGE bar.

Per-protocol set (PPS)–SIGE: All subjects in FAS-SIGE who do not violate the terms of the protocol in a way that would impact the study outcome. All decisions to exclude subjects for the PPS-SIGE will be made before the unblinding of the study.

The PK analysis set: All randomized subjects who received at least 1 dose of study drug with at least 1 measured PK concentration.

Immunogenicity analysis set: All randomized subjects who received any TAK-062 and have the baseline and at least 1 postbaseline immunogenicity sample assessment.

Efficacy Analysis:

Primary Efficacy Analysis: The primary efficacy analysis will be based on FAS-SIGE. The weekly CDSD GI symptom severity score is an average of the daily GI symptom severity scores during the week. The daily GI symptom severity score is the average of the severity score for diarrhea, abdominal pain, bloating and nausea, ranging from 0 (no symptoms) to 4 (very severe). Weekly CDSD GI symptom severity scores will be calculated where the CDSD is completed on at least 4 of the 7 days. When the daily diary is completed on less than 4 of the 7 days, the weekly CDSD GI symptom severity score will be considered missing. The attributes of the primary

estimand are:

- Population: Subjects with clinically active CeD and small intestinal villous atrophy who are experiencing inadvertent gluten exposure and meet all eligibility criteria.
- Variable/endpoint: Change in weekly CDSD GI symptom severity score from baseline to Week 12
- Treatments: TAK-062 ([redacted]) versus placebo.
- Intercurrent events (ICEs): Treatment discontinuation (due to adverse events [AEs] or other reasons), SIGE discontinuations, and use of rescue medications for CeD symptoms.

  Strategy for addressing ICEs: A composite strategy will be used to address rescue medication use and treatment discontinuation due to lack of efficacy or treatment-related AEs. For subjects who use rescue medications for CeD-related symptoms, the severity of the treated GI symptom(s) in CDSD on the days when the rescue medications are used will be set to very severe. For subjects who discontinue treatment due to lack of efficacy or treatment-related AEs, the Week 12 CDSD GI symptom severity score will be set to the baseline (Week -1) weekly CDSD GI symptom severity score. A treatment policy strategy will be used to address SIGE discontinuation (ie, the recorded weekly CDSD GI symptom severity scores will be used regardless of whether a subject has discontinued SIGE) and treatment discontinuation due to reasons other than lack of efficacy or treatment-related AEs.
- Population-level summary: Treatment difference (TAK-062 – placebo) in the mean change from baseline to Week 12 in weekly CDSD GI symptom severity score, for each dose level.

The primary endpoint will be analyzed with a mixed model for repeated measures (MMRM) approach using the appropriate contrast at Week 12. The model will be based on all available weekly CDSD GI symptom severity scores from Week -1 through Week 12. The model will include treatment group, week, treatment-by-week interaction, and the randomization stratification factors as fixed effects and baseline CDSD GI symptom severity score as covariates. An unstructured covariance structure will be used to model the within-subject errors. If the model does not converge, additional covariance structure will be used with the order specified in the statistical analysis plan (SAP). Two-sided tests comparing each of the TAK-062 dose groups with placebo at Week 12 will be conducted. The corresponding p-values, LS means of treatment differences and 2-sided 95% CI will be reported. The MMRM assumes data is missing at random. Sensitivity analysis will be performed with an alternative assumption that data is missing not at random. Supplementary analyses will be performed for the overall CDSD symptom severity score using the same approach as in the primary analysis.

Secondary Efficacy Analysis: The secondary efficacy analysis will be based on FAS-SIGE. The estimand framework corresponding to each secondary efficacy analysis has the same attributes in population, treatments, and ICEs as for the primary estimand. The variable/endpoint attributes for the secondary analysis are:

- Change in Vh:Cd from baseline (measured at Week -4) to Week 24.

The corresponding population-level summaries are:

- Treatment difference (TAK-062 – placebo) in the mean change from baseline (measured at Week -4) to Week 24 in Vh:Cd for each dose level.

The analysis will be conducted using analysis of covariance. The model will include treatment group and the randomization stratification factors as fixed effects and baseline values as covariate. Missing values will be regarded as missing at random. Missing data will be handled using multiple imputation (details will be provided in the SAP). The LS means and 2-sided 95% CI will be provided for the Week 24 treatment difference between the [redacted] TAK-062 dose groups versus placebo, respectively. Nominal 2-sided p-values will be provided for the comparison of [redacted] TAK-062 versus placebo, [redacted] TAK-062 versus placebo, and [redacted] TAK-062 versus placebo, respectively.

The placebo group includes all subjects randomized to receive placebo [redacted] and gluten-containing SIGE bar [redacted] in Cohorts 1 and 2 in all analyses unless specified otherwise.

Multiplicity Control: To control the overall Type I error rate for the primary efficacy endpoint, a fixed-sequence testing procedure will be used for the comparison of 3 doses of TAK-062 versus placebo. Specifically, the primary endpoint tested will be conducted in the following order:

i. First, [redacted] TAK-062 versus placebo for subjects taking gluten-containing SIGE.
ii. If the test in Step 1 is statistically significant, then perform the test comparing [redacted] TAK-062 versus placebo for subjects taking gluten-containing SIGE.
iii. If the test in Step 2 is statistically significant, then perform the test comparing [redacted] TAK-062 versus placebo for subjects taking gluten-containing SIGE.

Sample Size Justification:

The planned sample size is approximately 357 subjects. For a 2-sample comparison of means, 0.5 standardized mean difference is regarded as a medium effect size. A sample size of 53 subjects per treatment group will provide 80% power to detect a standardized mean difference (mean difference/SD) of 0.55 between [redacted] TAK-062 and placebo in the change from baseline in weekly CDSD GI symptom severity score (assuming a common SD) for a 2-sided statistical hypothesis test, using a 2-sample t-test and a 5% significance level. Assuming a dropout rate of approximately 12%, a sample size of 60 subjects per treatment group for the [redacted] and placebo arms in the gluten-containing SIGE group (Cohort 1) will be the planned enrollment.

The planned enrollment for Cohort 2 is 30 and 50 subjects per treatment arm in the placebo and active ([redacted] TAK-062) respectively, in the gluten-containing SIGE arms; 50 subjects (43 adults and 7 adolescents) per arm in the [redacted] and placebo gluten-free SIGE bar arms; and 7 subjects (adolescents only) in the [redacted] gluten-free SIGE bar arm. The analysis to detect the difference between the combined placebo gluten-containing SIGE group and the active group would yield a higher power.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform oversight of all study-related activities. Qualified vendors will be identified to perform study-related activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda may 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 drug, 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 and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
Cd	crypt depth
CDAQ	Coeliac Disease Assessment Questionnaire
CD-QoL	celiac disease quality of life
CDSD	Celiac Disease Symptom Diary
CeD	celiac disease
CeD-GSRS	Celiac Disease Gastrointestinal Symptom Rating Scale
CFR	Code of Federal Regulations
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DGP	deaminated gliadin peptide
ECG	Electrocardiogram, electrocardiographic
eCRF	electronic case report form
EGD	esophagogastroduodenoscopy
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFD	gluten-free diet
GFR	glomerular filtration rate
GI	gastrointestinal
GIP	gluten immunogenic peptide
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HLA	human leukocyte antigen
HRQOL	health-related quality of life
IA	interim analysis
IB	investigator's brochure
ICDSQ	Impact of Celiac Disease Symptoms Questionnaire
ICE	intercurrent event
ICH	International Conference on Harmonisation
ID	identification (number)
IDMC	independent data monitoring committee
IEC	independent ethics committee
IEL	intraepithelial lymphocyte

INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NAb	neutralizing antibody
NOAEL	no-observed-adverse-effect level
PAP	psychometric analysis plan
PCR	polymerase chain reaction
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PPS	per-protocol set
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PTE	pretreatment event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SF-12	Short Form 12-Item
SIGE	simulated inadvertent gluten exposure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
tTg	tissue transglutaminase
ULN	upper limit of normal
US	United States
v	Version
VCE	video capsule endoscopy
Vh	villous height
Vh:Cd	villous height–to–crypt depth ratio
WOCBP	woman of childbearing potential
WPAI+CIQ:CeD	Work Productivity and Activity Impairment Plus Classroom Impairment Questionnaire: Celiac Disease

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

Despite attempts to maintain a gluten-free diet (GFD), many individuals with celiac disease (CeD) continue to have symptoms and/or intestinal damage due to gluten exposure. TAK-062 is a computationally designed enzyme intended to reduce or prevent symptoms and intestinal damage related to gluten exposure (Pultz et al. 2021). TAK-062 is being investigated as an adjunct to a GFD for the treatment of moderate to severe symptomatic CeD in patients with inadequate response to dietary modifications and signs of small intestine mucosal injury. The primary goal of this study is to assess the efficacy and safety of TAK-062 for treatment of symptoms and intestinal damage related to inadvertent gluten exposure in subjects with CeD. To robustly assess protection from real-world gluten exposure, the study will use food bars containing a small amount of gluten, referred to as simulated inadvertent gluten exposure (SIGE).

The study will have 2 cohorts; in Cohort 1, safety and efficacy of TAK-062 will be evaluated in adult subjects at the highest dose ([redacted]) in the presence of SIGE; in Cohort 2, safety and efficacy of TAK-062 will be evaluated at 3 doses ([redacted]) in adults with gluten-containing and gluten-free SIGE and at 2 doses ([redacted]) in adolescent subjects with gluten-free SIGE. The interim analysis (IA) will be initiated when at least 75% of the subjects in Cohort 1 have either completed 12 weeks of treatment or have dropped out, to determine inclusion of adolescents in Cohort 2. Cohort 1 data will be reviewed by an external independent data monitoring committee (IDMC) and shared with health authorities and independent ethics committees (IECs)/institutional review boards (IRBs) as required by region, before enrollment of adolescents in Cohort 2. If efficacy and safety data from Cohort 1 is considered acceptable, Cohort 2 will also include adolescents aged 12 to 17 years, inclusive. Adolescents will receive only gluten-free SIGE bars.

In addition, this study has 3 other important goals:

1. Evaluation of the psychometric properties of the Celiac Disease Symptom Diary (CDSD) Version (v)2.1. The CDSD has been developed specifically for CeD. This study will include additional patient-reported outcomes (PROs) such as the Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and Celiac Disease Gastrointestinal Symptom Rating Scale (CeD-GSRS) to facilitate psychometric evaluation of the CDSD, which may enable the CDSD to be used as a primary endpoint in future studies. Results from CDSD psychometric assessment will be reported in a separate psychometric report.
2. To provide data on the optimal histologic measure for assessment of response to treatment in CeD. While there is consensus that assessment of change in small intestinal mucosal injury and intraepithelial lymphocyte (IEL) infiltration is important in studies of CeD treatment, the optimal histologic endpoint for use in clinical studies is unclear. This study will assess the utility of quantitative and qualitative histologic endpoints (eg, IEL counts, villous height

[Vh], crypt depth [Cd], villous height–to–crypt depth ratio [Vh:Cd], Marsh-Oberhuber score) to inform future studies.

- [redacted]

4.1.1 Disease State Background

CeD is a multisystem autoimmune disease triggered by ingestion of dietary gluten in genetically susceptible individuals (Ludvigsson et al. 2013). Deamidated gluten peptides can bind with high affinity to human leukocyte antigen (HLA)-DQ2/DQ8 on antigen-presenting cells, which elicits T cell-driven cytotoxic and antibody-mediated immune responses. Intestinal injury is predominantly cell-mediated and characterized by villous atrophy, crypt hyperplasia, and infiltration of lymphoid cells into both the epithelium and lamina propria. CeD is one of the most common immune-mediated gastrointestinal (GI) diseases and can affect individuals at any age, although most diagnoses occur in late adolescence and early adulthood.

Currently, there are no approved therapies for CeD and the only option for patients is a GFD that involves strict lifelong avoidance of exposure to >20 ppm of gluten proteins from wheat, barley, and rye as stipulated by The Codex Standard for Foods for Special Dietary Use for Persons Intolerant to Gluten (Codex Alimentarius 2015). The threshold of daily gluten that will cause mucosal injury in both adults and children is thought to be 10 to 50 mg/day, or about one-hundredth of a slice of bread (Catassi et al. 2007; Gibert et al. 2013). However, there are reports of patients where even a single milligram of gluten, an amount impossible to avoid in daily life, can prevent adequate clinical disease control (Biagi et al. 2004).

The majority of patients report frequent symptoms related to gluten exposure despite attempts at gluten avoidance (Hall et al. 2013). More than 70% of patients with CeD are not satisfied with the GFD due to the combination of ongoing symptoms and/or high burden of maintenance of lifelong strict dietary restriction (Barratt et al. 2011).

Disease control attained with the GFD has traditionally been grouped into 3 categories. The first category is responsive disease whereby dietary modification results in resolution of small intestine mucosal injury and infrequent or minor ongoing symptoms and represents 70% of the CeD population. The majority of the remaining 30% of the CeD population fall into the second category and have what is known as persistently active CeD, which is defined by ongoing symptoms and/or small intestine mucosal injury despite dietary modification (Leonard et al. 2017). The most common reason for persistently active CeD is inadvertent gluten exposure. It is these patients, with ongoing symptoms and intestinal damage felt to be related to gluten exposure, who are the intended subjects in this study. Less than 1% of patients have refractory

CeD, the third category, in which there are ongoing severe symptoms and small intestine mucosal injury despite demonstrated gluten avoidance.

4.2 Rationale for the Proposed Study

Phase 1 studies have demonstrated robust gluten digestion, acceptable pharmacokinetic (PK) characteristics and no safety concerns to date. This study will be the first phase 2 study to test the efficacy and safety of TAK-062 in subjects with CeD on a GFD.

4.3 Benefit-Risk Profile

Oral enzyme supplementation with a highly effective glutenase has the potential to meet a significant unmet medical need for a pharmacologic intervention used as an adjunct to a GFD. In particular, given its ability to effectively and rapidly degrade gluten in vitro and in vivo, as well as its favorable safety profile in clinical and nonclinical studies to date, further development of TAK-062 for subjects with CeD is warranted.

Repeat-dose nonclinical studies have shown no TAK-062–related toxicity up to the highest evaluated dose of 2000 mg/kg/day (limit dose) in both rats (up to 6 months) and monkeys (up to 13 weeks), and no effects on embryofetal development in the rat or rabbit (see IB for further detail). Based on the human equivalent dose the no-observed-adverse-effect level (NOAEL) of 1000 mg/kg administered orally twice per day (2000 mg/kg/day) in the 6 month general toxicity study in the rat and the 13-week general toxicity studies in the cynomolgus monkey, this provides a margin of 10.8 and 21.5 relative to the proposed high dose of [redacted] in humans, respectively.

Antidrug antibodies (ADAs) were seen in nonclinical studies but are not considered predictive for the development of ADAs in humans. Clinical ADAs were nonneutralizing, not associated with adverse event (AE), and had no measurable impact on gluten degradation. Development of ADA to TAK-062 liquid and capsule formulations was evaluated in Parts 1 and 2, and development of ADA to TAK-062 tablet formulation was evaluated in Parts 3 and 4 of the phase 1 clinical study (PvP-102-01).

Currently, there are no important identified or important potential risks associated with TAK-062 treatment based on the evidence from phase 1 clinical studies and nonclinical toxicology studies. However, ADA is considered a potential risk with the administration of TAK-062 based on limited data in the phase 1 clinical trial, and this will be monitored in this study and future studies. Cohort 1 data will be reviewed by an external IDMC and shared with health authorities and IECs/IRBs as required by region, before enrollment of adolescents. If efficacy and safety data from Cohort 1 is considered acceptable, Cohort 2 also will include adolescents aged 12 to 17 years, inclusive. Adolescent subjects will be randomized into the gluten-free SIGE groups only.

Potential risks are based on symptoms related to gluten exposure and testing related to study endpoints. These include the following:

- Phlebotomy: There is minimal risk associated with phlebotomy (limited to <500 mL) in otherwise healthy adults.
- Endoscopy with duodenal biopsy: endoscopy with duodenal biopsy is a common GI procedure. Risks include those related to procedural sedation, the endoscopic procedure, and the biopsies. Cumulatively, the risks of upper endoscopy are estimated to be <0.5% (Levy and Gralnek 2016). Clinical evaluation of subjects before endoscopy will be completed according to established site protocols.

[redacted]

In summary, there have been no safety signals and no important identified or important potential risks associated with TAK-062 treatment based on the data from phase 1 clinical studies and toxicology studies to date.

- The development of ADA is a potential risk.
- There has been 1 unrelated serious adverse event (SAE) reported across the clinical program to date.
- There was no evidence of systemic exposure to TAK-062 liquid and capsule formulations after treatment with any dose administered in phase 1 studies.
- There are no AE designated as AEs of special interest for TAK-062.
- AEs and SAEs will continue to be routinely monitored in ongoing studies and future studies.

Overall, the phase 1 and nonclinical study results are not suggestive of any safety risks related to TAK-062 for the ongoing development program; the benefit-risk profile is, therefore, considered appropriate to support the continuation of the clinical development program for TAK-062 for CeD indication as planned.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the efficacy of TAK-062, as measured by the CDSD, for reducing celiac-related symptoms due to gluten exposure in subjects with CeD attempting to maintain a GFD in treated subjects versus placebo controls.

5.1.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of TAK-062 for improvement of small intestine mucosal injury due to gluten exposure in subjects with CeD attempting to maintain a GFD in treated subjects versus placebo controls.
- To evaluate the safety and tolerability of TAK-062.

5.1.3 Exploratory/Additional Objectives

The exploratory/additional objectives of this study are:

- To further evaluate the psychometric properties of the CDSD in symptomatic subjects with CeD.
- To evaluate the efficacy of TAK-062 on reducing their most bothersome symptom.
- To evaluate the treatment effect of TAK-062 on IEL counts and quantitative and qualitative histological measures of disease severity.
- To evaluate immunogenicity to TAK-062.
- To evaluate the effect of TAK-062 on quality of life and additional PROs.
- To evaluate the effect of TAK-062 on celiac serology titers.
- To evaluate the relationship between PROs and histological measures of intestinal injury.
- To evaluate the effect of SIGE on response to therapy with TAK-062.
- To evaluate urine gluten immunogenic peptide (GIP) detection as a means of monitoring gluten exposure and response to therapy.

[redacted]

[redacted]

- To characterize the PK of TAK-062 in subjects with CeD attempting to maintain a GFD.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is:

- Change in weekly CDSD GI symptom severity score from baseline (Week -1) to Week 12.

5.2.2 Secondary Endpoint

The secondary endpoint is:

- Change in Vh:Cd from baseline (measured at Week -4) to Week 24.

5.2.3 Safety Endpoints

Treatment-emergent adverse events (TEAEs), SAEs, treatment-related TEAEs, electrocardiographic (ECG) findings, vital signs, laboratory parameters, and immunogenicity (posttreatment, positive ADA in serum for TAK-062).

5.2.4 Exploratory/Additional Endpoints

Exploratory/additional endpoints (baseline assessments made [redacted] unless specified otherwise) are:

Impact of SIGE:

- Differences in responses in CeD endpoints including PROs, celiac serology, histology [redacted] will be assessed between SIGE and gluten-free SIGE bar arms.

PRO Outcomes:

- Change in CDSD GI symptom severity score from Week -8 and Week -1 to Week 24.
- Change in CDSD GI symptom severity score from Week -8 to Week 12.
- PGIC at Weeks 0, 12, and 24.
- Percent of subjects reporting each symptom on the CeD Most Bothersome Symptom Questionnaire at each time point measured.
- Change from Week -8 and Week -1 to Week 12 and Week 24 in the following PROs:
  - Weekly score of the most bothersome symptom as reported by the CDSD.
  - Severity rating or frequency of each item (symptom) of the CDSD.
  - Frequency of constipation based on the CDSD.
  - Proportion of minimal symptom days per week (defined as days with none or no more than 1 mild score of either bloating, abdominal pain, nausea, or diarrhea) as reported on the CDSD.
  - Proportion of symptom-free days per week as reported on the CDSD.

- Impact of Celiac Disease Symptoms Questionnaire (ICDSQ).
- PGIS.
- Patient-Reported Outcomes Measurement Information System (PROMIS)—Cognitive Function Instrument.
- PROMIS—Fatigue Instrument.
- Short Form 12-Item (SF-12) Health Survey.
- EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) health survey.
- Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Celiac Disease (WPAI+CIQ: CeD).
- CeD-GSRS.
- Coeliac Disease Assessment Questionnaire (CDAQ).
- Celiac disease quality of life (CD-QoL) questionnaire.

Serology titers:

- Change from baseline (Week -8) to Week 24 in celiac serology titers.

Histological endpoints:

- Proportion of subjects achieving mucosal remission (Vh:Cd ≥3) at Week 24.
- Change from baseline (Week -4) to Week 24 in IEL counts.
- Change from baseline (Week -4) to Week 24 in Marsh-Oberhuber scores, both qualitatively assessed and calculated from IEL and Vh:Cd results.
- Change from baseline (Week -4) to Week 24 in individual Vh and Cd measurements.
- Proportion of subjects with an increase of ≥0.5, ≥0.75, and ≥1 in Vh:Cd from baseline (Week -4) to Week 24.

[redacted]

GIP endpoints:

- Frequency of positive urine GIP tests in subjects across the different treatment groups.

PK

- Plasma concentration of TAK-062.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a 2-cohort phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of multiple dose levels of TAK-062 for the treatment of ongoing symptoms and small intestinal mucosal injury due to gluten exposure in subjects with CeD attempting to maintain a GFD. In addition, this study is designed to further evaluate the psychometric properties of the CDSD [redacted]

Cohort 1 will have approximately 120 adult subjects. After the IA, a decision will be made by the sponsor on whether to begin enrollment of adolescents in Cohort 2. Cohort 1 data will be reviewed by an external IDMC and shared with health authorities and IECs/IRBs as required by region, before enrollment of adolescents in Cohort 2. If efficacy and safety data from Cohort 1 is considered acceptable, Cohort 2 will also include adolescents aged 12 to 17 years, inclusive after IDMC review at IA. If initiated, Cohort 2 will include approximately 216 adults and 21 adolescents aged 12 to 17 years, inclusive.

In Cohort 1, all subjects will consume gluten-containing SIGE bars [redacted] with a meal [redacted]). In Cohort 2, adult subjects will receive either gluten-containing or gluten-free SIGE bars, [redacted] with a meal throughout the treatment period. [redacted]. On-study gluten intake will be assessed by measuring GIP in urine. It is expected that SIGE will result in stable, rather than worsening, symptoms [redacted] and in the placebo groups. Adolescents in Cohort 2 will receive only gluten-free SIGE bars.

Cohort 1 (120 adults)

Cohort 1 will consist of 120 adult subjects randomly assigned to receive 1 of 2 treatments:

1. TAK-062 placebo [redacted] + gluten-containing SIGE bar [redacted]: 60 subjects.
2. TAK-062 [redacted] + gluten-containing SIGE bar [redacted]: 60 subjects.

Cohort 2 (216 adults and 21 adolescents)

Cohort 2 will consist of approximately 237 subjects overall. Approximately, 216 adult subjects to be enrolled and randomly assigned into 1 of 5 study drug and SIGE treatment groups (Groups 1-5), and approximately 21 adolescent subjects to be enrolled and randomly assigned into Groups 4, 5, and 6 (adolescents only).

1. TAK-062 placebo [redacted] + gluten-containing SIGE bar [redacted]: 30 subjects (adults only).

2. TAK-062 [redacted] + gluten-containing SIGE bar [redacted]: 50 subjects (adults only).
3. TAK-062 [redacted] + gluten-containing SIGE bar [redacted]: 50 subjects (adults only).
4. TAK-062 placebo [redacted] + gluten-free SIGE bar [redacted]: 50 subjects (43 adults, 7 adolescents).
5. TAK-062 [redacted] + gluten-free SIGE bar [redacted]: 50 subjects (43 adults, 7 adolescents).
6. TAK-062 [redacted] + gluten-free SIGE bar [redacted]: 7 subjects (adolescents only).

The study period will consist of 4 periods in each cohort: a 2- to 4-week screening period, a 4-week single-blind placebo run-in, a 24-week double-blind treatment period, and a 4-week safety follow-up period. At the first visit (Week -8), the subject will consume 1 gluten-free SIGE bar, and will be excluded if they develop significant symptoms suggesting a confounding nongluten food intolerance. During the screening period (between Week -8 visit to Week -4 visit), subjects will complete the CDSD daily to confirm they have at least 1 ongoing CeD-related GI symptom of moderate or greater severity on at least 3 days out of any consecutive 7-day period. The CeD-related symptom(s) may vary day by day as long as the severity of at least 1 symptom is moderate or greater. Eligible subjects will undergo an esophagogastroduodenoscopy (EGD) with duodenal biopsy [redacted] for the assessment of villous atrophy.

In addition, a subset of approximately 40 subjects in total that provide a wide range of villous injury [redacted]

During the single-blind run-in period (Week -4 through Day -1), subjects will receive TAK-062 placebo [redacted] and complete the CDSD daily. [redacted] While all efforts should be made to obtain weekly urine samples, missed urine GIP samples will not be considered a protocol deviation.

Eligible subjects with villous atrophy on duodenal biopsy (defined as Vh:Cd <2.5 by central pathology assessment) will be randomly assigned to 1 of 2 (Cohort 1) or 1 of 6 (Cohort 2) treatment groups described above to receive double-blind treatment and SIGE or gluten-free SIGE (Cohort 2) treatment for 24 weeks (Day 1 through Week 24). Initially, all subjects who

meet symptom criteria and histologic criteria will be randomized. If more than 10% of planned enrollment in a cohort report a greater than 1 point improvement in PGIS during [redacted] run-in period (Week -2 through Day -1), further subjects showing this degree of improvement will be excluded from the cohort.

Randomization will be stratified by celiac serologic status at Visit 1, defined as normal or elevated celiac serology (1 or more of the following: IgA-tissue transglutaminase (tTg) >1 × the upper limit of normal [ULN], IgA–deaminated gliadin peptide [DGP] >2 × ULN, or IgG-DGP >2 × ULN), mild to moderate (Vh:Cd 1.5 to <2.5) versus moderate to severe (Vh:Cd <1.5) histologic injury at baseline, and by use of proton pump inhibitors (PPIs) or histamine 2 antagonists (yes or no) at Visit 1.

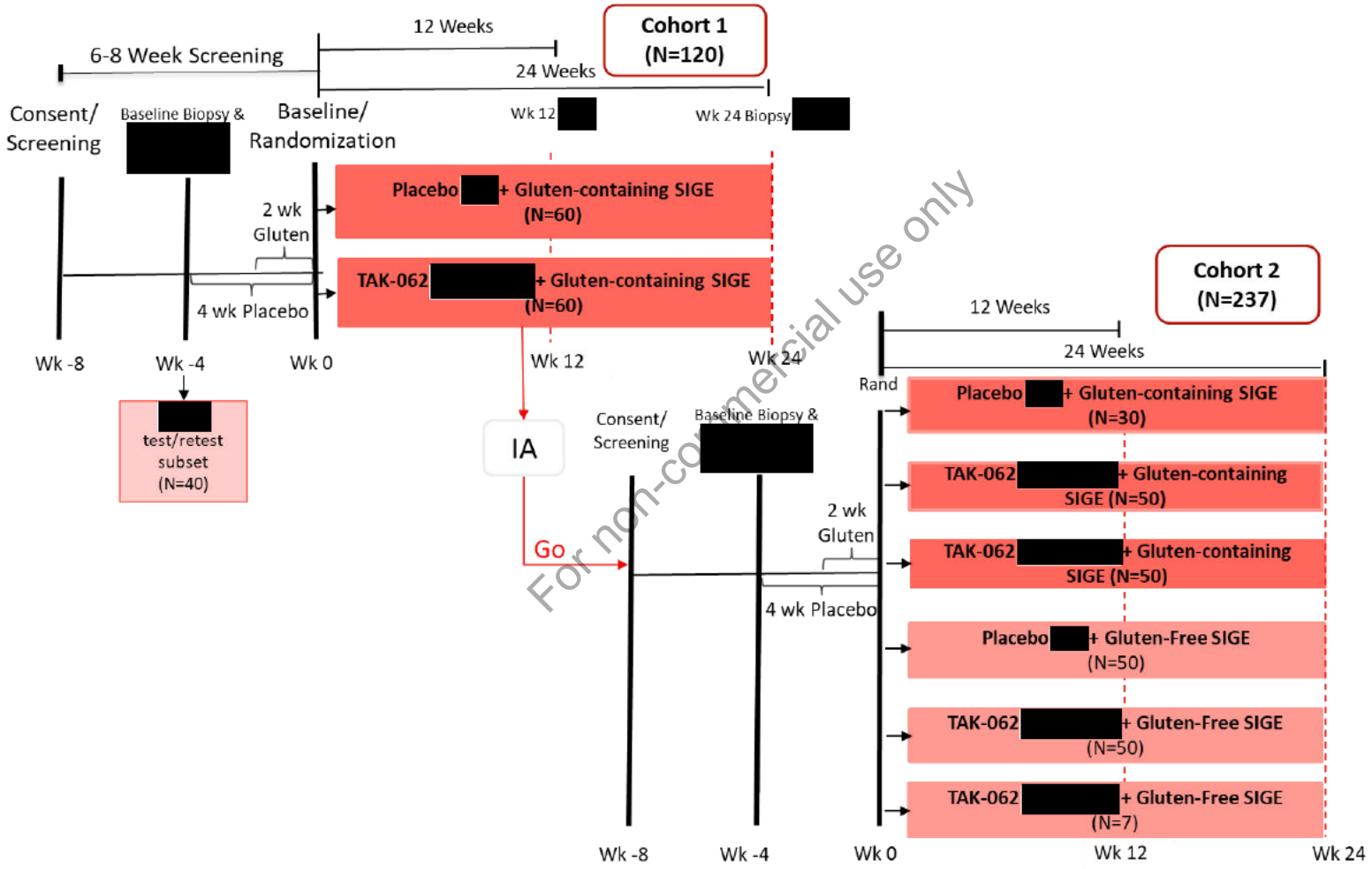
Subjects will report symptoms daily using the CDSD from Week -8 through Week 24.

EGD with biopsy will again be performed at the end of the 24-week treatment period (Week 24). [redacted]

Sparse blood samples to evaluate the PK of TAK-062 in plasma will be collected in all subjects at Weeks -4, 0, 3, 12, 24, and 28. Approximately 10 adult subjects enrolled in Cohort 1, and 30 adult subjects enrolled in Cohort 2 will participate in the PK subgroup for slightly more intensive collections at the Week 0 (randomization) and Week 3 visits. Predose plasma and serum collections will be done at these same clinic visits for exploratory analysis of circulating biomarkers. There is a safety follow-up visit at Week 28, 4 weeks after the last date of treatment.

Diagrams of the study design are included as Figure 6.a and a Schedule of Study Procedures is listed in Appendix A.

Figure 6.a Schematic of Study Design



EGD: esophagogastroduodenoscopy; EOT: end of treatment; IA: interim analysis; SIGE: simulated inadvertent gluten exposure; [redacted]; [redacted]; Wk: week.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Rationale for Study Design

Three TAK-062 doses versus placebo will be evaluated in this study with a primary outcome of improvement in symptoms as measured by the CDSD along with secondary outcomes of change in small intestinal mucosal injury in subjects treated with TAK-062 compared with placebo (Leffler et al. 2015; Murray et al. 2017). This study will enroll subjects who have been attempting to maintain a GFD for at least 12 months, who have ongoing GI symptoms as measured by the CDSD, and have small intestine villous atrophy on duodenal biopsy. The use of SIGE bars [redacted] double-blind treatment periods is [redacted] The study will enroll 2 cohorts; Cohort 1 will evaluate safety and efficacy of TAK-062 in adult subjects with the highest dose in the presence of SIGE bar consumption; Cohort 2 will evaluate safety and efficacy of TAK-062 at 3 doses ([redacted]) in adults with gluten-containing or gluten-free SIGE bar consumption. In addition, there will be 2 doses ([redacted]) in adolescent subjects with gluten-free SIGE bar consumption. The run-in period will be followed by 24 weeks of double-blind treatment with placebo or TAK-062. Subjects will be given low doses [redacted] of gluten or gluten-free SIGE in the form of a food bar throughout the study in a double-blind manner [redacted] because prior CeD studies have demonstrated a very large clinical study effect due to both placebo response and reduced gluten exposure.

Randomization, placebo control, and blinding are regarded as the gold standard design elements for minimizing potential biases. The factorial design allows the efficient evaluation of effects of study treatment, SIGE, and their interaction. Because the treatment effect of SIGE is expected to be small, only [redacted] TAK-062 and placebo are planned to be evaluated with gluten-free SIGE. The effect of [redacted] TAK-062 is assumed to be no larger than the effect of [redacted] TAK-062 under gluten-free SIGE.

The run-in period will establish subject's baseline results for efficacy evaluation, [redacted]

6.2.2 Rationale for Dose

TAK-062

To date, repeat-dose nonclinical studies for TAK-062 have shown no toxicity up to the limit dose and NOAEL of 2000 mg/kg/day. Calculation of the human equivalent dose applied to the observed NOAEL of 2000 mg/kg/day after a 10-fold safety factor was 1938 mg TAK-062 liquid formulation based on rat and 3870 mg TAK-062 liquid formulation based on monkey. Doses of [redacted] tested in phase 1 studies were well-tolerated and these doses are all less than half of the NOAEL. Safety data showed that TAK-062 was well-tolerated up to [redacted]. AEs were of mild to moderate severity, not drug-related, and most commonly related to nasogastric tube placement. There has been 1 unrelated SAE reported across the clinical program to date. An in vitro experiment showed that [redacted] dose of TAK-062 liquid formulation exhibited greater activity than the [redacted] dose during the first 30 minutes. In the phase 1 study, the gluten degradation activity of TAK-062 was assessed in healthy subjects receiving placebo and [redacted] of liquid formulation before 1 g of gluten; or placebo and [redacted] of liquid formulation before 6 g of gluten. The percentage of gluten degraded relative to placebo was found to be comparable across [redacted] doses, suggesting the digestion of immunogenic gluten peptides of TAK-062 was similarly effective at this dose range. On the basis of these results, the dose levels of [redacted] were selected to explore the therapeutic benefit and efficacious dose range of TAK-062.

TAK-062 is dosed [redacted] before the start of a meal because the site of action is in the stomach and it is expected that the enzyme will pass out of the stomach within 4 hours after administration.

SIGE

Inclusion of SIGE in this study serves 2 main purposes. First, [redacted]. TAK-062 works only on gluten, so it is essential that gluten be consumed to assess therapeutic efficacy. In prior CeD studies that did not include SIGE, significant improvements in symptoms and/or histology were observed in the placebo arms (Leffler et al. 2015; Murray et al. 2017). This effect has been attributed, at least in part, to reduction in gluten exposure as a result of trial participation (Stefanolo et al. 2020). Second, if a positive therapeutic effect is observed, then the inclusion of SIGE, [redacted] provides confidence that the effect seen in the study will confer real benefit to patients outside of a study where gluten exposures are known to be highly variable.

Subjects will consume [redacted] with a meal for the duration of the study [redacted] in subjects randomized to gluten-containing bars. The typical result of this exposure is anticipated to be stable symptoms from initial screening in the placebo cohort rather than exacerbation of symptoms.

Emerging data have suggested that even in patients adherent to a GFD, [redacted]

While the administration of SIGE is not anticipated to exacerbate CeD-related symptoms, in situations where the administration of SIGE may confound the clinical evaluation of a GI condition that arises during the treatment period, investigators may temporarily cease administration of SIGE up to a maximum of 2 weeks, following discussion with the study medical monitor. If cessation of SIGE during the treatment period extends beyond 2 weeks, the subject will be withdrawn from the treatment arm due to lack of efficacy and continued in the study for monitoring and safety. Any investigator-determined cessation of SIGE administration must be recorded in the appropriate electronic case report form (eCRF).

The adolescent group in Cohort 2 will not be exposed to SIGE because this group will be randomized only into the gluten-free SIGE group.

6.2.3 Rationale for Endpoints

6.2.3.1 *Efficacy*

The goal of TAK-062 is to show improvement of ongoing GI symptoms and small intestinal mucosal injury due to gluten exposure in patients with CeD. Efficacy will be evaluated primarily through the demonstration of the clinical benefit of treatment as an adjunct to the GFD. Through this study, Takeda expects to develop a robust understanding of the dose of TAK-062 necessary to improve ongoing symptoms and intestinal pathology related to active CeD.

The primary endpoint will be reduction in mean weekly CDSD score in TAK-062 treatment group versus placebo. Because ongoing active CeD is experienced by subjects as symptoms, symptom improvement is an appropriate basis of establishing effectiveness of therapies that are adjunctive to a GFD.

The CDSD measures GI symptoms on a daily basis and was developed in accordance with Food and Drug Administration (FDA) guidance on PRO measures (Patrick et al. 2007). This measure allows for sensitive measurement of episodic episodes of symptoms; however, the CDSD is not yet validated for the intended context of use. To assess the psychometric properties of the CDSD, anchors (PGIS and PGIC) will be used to assess the meaningful within-patient change. Additional measures of celiac-related symptoms will also be assessed (eg, CeD-GSRS and PROMIS—Fatigue Instrument) to measure convergent validity.

6.2.3.2 Tissue-Based Biomarkers: Vh:Cd and IELs

As a complement to understanding how subjects are feeling during the study, a secondary endpoint of this study will be the change in Vh:Cd ratio on duodenal biopsy from baseline (Week -4) to the end of treatment. The Vh:Cd ratio represents mucosal architectural changes and a lower Vh:Cd ratio indicates more severe intestinal injury characterized by a flattening of the mucosa. Changes in the individual Vh and Cd measurements will also be evaluated as exploratory endpoints. Because ongoing small intestinal mucosal injury is a major risk factor for long-term complications, showing improvement in tissue histology is necessary for establishing effectiveness of therapies that are adjunctive to a GFD. Additionally, increases in IELs are often monitored as a marker of inflammation in the duodenal epithelium. The ability of TAK-062 to affect these histological markers will be important endpoints monitored in this study.

Other Exploratory Biomarkers

Exploratory analysis of intestinal gene expression (RNA) and tissue microbiome community may also be done but will not be a part of the clinical study report. Predose plasma and serum samples are also being collected to enable evaluation of novel circulating biomarkers under investigation and how they respond to treatment. These include microbial identification, exosome quantification, proteomic analysis, and quantitation of markers of extracellular matrix remodeling. These collections may be useful for noninvasive patient selection or disease monitoring.

6.2.3.3 [redacted]

[redacted]

6.2.3.4 Urine-Based Biomarker: GIP

As a means of monitoring gluten exposure during the study, urine samples will be collected in standard urine collection cups once per week for evaluation of GIP using a qualitative assay. To enable quantitative detection of different gluten peptides, subjects will collect urine in [redacted] on the day of a clinic visit and take the sample to the site. [redacted] While all efforts should be made to obtain weekly urine samples, missed urine GIP samples will not be considered a protocol deviation.

Ingested gluten is degraded into immunostimulatory peptides that can be detected in urine. Measurements will be taken at screening to understand if any potential subjects have evidence of active gluten exposure and then during the run-in period, at baseline, and all other study visits to monitor gluten exposure before and during study execution. Results will support conclusions regarding the gluten degrading capability of TAK-062.

6.2.3.5 Safety

Safety will be monitored on the basis of the occurrence of TEAEs, SAEs, physical examination findings (in the context of AEs), vital signs (heart rate, blood pressure, temperature, respiration rate), ECGs, and clinical laboratory parameters (chemistry, hematology, and urinalysis). A serum pregnancy test will be conducted at screening and urine pregnancy tests at all other scheduled visits before receiving study drugs for women of childbearing potential (WOCBP). All TEAEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of TAK-062 that indicates a change in the currently known benefit-risk profile such that the benefit-risk balance is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

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

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/IECs are notified as appropriate.

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. The subject is able to provide written informed consent form to participate in the study before completing any study-related procedures.
2. In the opinion of the investigator, the subject is willing and fully capable of understanding and complying with study procedures including PRO compliance and restrictions defined in this protocol.
3. The subject has an adequate comprehension of a GFD assessed by the site investigator after review of responses to a knowledge test. The final determination of a subject's adequate comprehension of a GFD is at the discretion of the investigator.
4. The subject has at least 1 CeD-related GI symptom of moderate or greater severity, as measured by the CDSD, on at least 3 days out of any consecutive 7-day period during the screening period (Week -8 visit until Week -4 visit), felt by the investigator to be related to gluten exposure. The CeD-related symptom(s) may vary day by day as long as the severity of at least 1 symptom is moderate or greater. The subjects must meet symptom criteria to undergo EGD/VCE.
5. The subject has biopsy-confirmed CeD or, in subjects with CeD without a producible initial biopsy report, the following additional inclusion criteria must be met:
   a) Serology (IgA-tTg) at diagnosis or subsequent visit must be at least 2 times the ULN.
   b) Histology at screening biopsy at Week -4 must be consistent with Marsh-Oberhuber score of 2 or greater as read by a central pathologist.
6. The subject has been attempting to maintain a GFD for at least 12 months as self-reported by the subject.
7. The subject has small intestinal villous atrophy on duodenal biopsy defined as Vh:Cd <2.5 at Week -4.
8. The subject is HLA-DQ2 and/or HLA-DQ8 positive.
9. The subject in Cohort 1 is aged 18 years and older at the time of signing the informed consent form. Inclusion of subjects older than 75 years of age will require discussion with the study medical monitor prior to enrollment.
10. The subject in Cohort 2 is aged 12 and older at the time of signing the informed consent/pediatric assent forms. Subjects 12 to 17 years of age, inclusive, will only be included after IDMC review at IA. Inclusion of subjects older than 75 years of age will require discussion with the study medical monitor prior to enrollment.
11. The subject is in a good general state of health according to clinical history and physical examination, in the opinion of the investigator.
12. The subjects must have a body mass index (BMI) between 16 and 45, inclusive.

Note: Individuals with BMI of 40 to 45 should be discussed with the medical monitor and confirmed to be appropriate for endoscopy according to local site guidelines.

13. The subject is willing and able to continue any current dietary and/or medical regimens (including gastric acid suppression) in effect at the first visit (Visit 1). There should be no changes to diet, medications (prescription or over-the-counter) or supplements during study participation.
14. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use an effective method of contraception (Section 9.3.13) from signing of informed consent/pediatric assent forms throughout the duration of the study and for 100 days after last dose of study drug.
15. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use an effective method of contraception* from signing of informed consent/pediatric assent forms throughout the duration of the study and for 40 days after the last dose of study drug.

*Definitions and effective methods of contraception are defined in Section 9.3.13 and reporting responsibilities are defined in Section 9.3.14.

7.2 Exclusion Criteria

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

1. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
2. The subject has inadequate renal or hepatic function before randomization based on the following laboratory parameters:
   - Total bilirubin ≥1.5 × ULN unless the subject has known Gilbert's syndrome that can explain the elevation of bilirubin, or
   - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 × ULN, or
   - Glomerular filtration rate (GFR) <49 mL/min. For subjects with GFR 49 to 59 mL/min, inclusion determination should be discussed with the sponsor.

   Note: The subjects may be retested (1 time) to meet eligibility criteria at the discretion of the investigator.
3. The subject has 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 medication.

- 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 include systemic autoimmune disease such as scleroderma, psoriatic or rheumatoid arthritis, or lupus that is stable and without GI involvement; well-controlled autoimmune thyroid disease; well-controlled type 1 diabetes; or PPI-responsive eosinophilic esophagitis in symptomatic and histologically confirmed remission.

4. The subject has ongoing systemic immunosuppressant, systemic corticosteroid treatment excluding medication given for the endoscopies, or treatment with systemic immunosuppressants or systemic corticosteroids in the 12 weeks before screening.
   - The subject is receiving immunosuppressive doses of corticosteroids: 3 mg per day or more of budesonide for more than 3 consecutive days within 3 months before screening, more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more within 90 days before the first dose, any dose of oral or IV corticosteroids within 30 days of the first dose, or high-dose inhaled corticosteroids (>960 µg/day of beclomethasone dipropionate or equivalent), or other systemic immunosuppressive agents.
5. The subject has ongoing use of over-the-counter digestive enzymes or digestive supplements, other than lactase, including those for gluten digestion. Probiotics are allowable if they were started before screening and not discontinued or changed in dose or type during the study.
6. The subject has an inability to swallow the study drug tablet.
7. The subject has completed the CDSD on ≤75% of the evaluable days during the run-in period until randomization.
8. If more than 10% of planned enrollment in a cohort report a greater than 1 point improvement in PGIS during [redacted] run-in period (Week -2 through Day -1), further subjects showing this degree of improvement will be excluded from the cohort.
9. The subject has ongoing symptoms that are considered by the investigator to be due to other GI conditions, including irritable bowel syndrome, small intestinal bacterial overgrowth, and eosinophilic disorders.
10. The subject has active microscopic colitis requiring treatment in the 6 months before screening.
    - Microscopic colitis detected at screening if sigmoidoscopy is performed would exclude the subject.
11. The subject has known or suspected type 2 refractory CeD or ulcerative jejunitis.
12. The subject has ongoing chronic use (defined as >7 days continuous use) of a nonsteroidal anti-inflammatory drug aside from <100 mg aspirin, daily, for prophylactic use.

13. The subject has ongoing use, or use in the 3 months before screening, of medications known to cause villous abnormalities (eg, mycophenolate mofetil, angiotensin receptor blockers, colchicine).
14. The subject used treatments for GI symptoms including antiemetics, antidiarrheals, antispasmodics, medical marijuana (use of medical marijuana indicated for non-GI conditions is not exclusionary) within 2 weeks of screening and during the run-in period. Subjects on stable doses (ie, more than 4 weeks) of an osmotic, bulking-forming or emollient (surface active agent) laxative are eligible, provided symptoms are considered not related to CeD in the opinion of the investigator.
15. The subject has a known or suspected severe enteric infection (viral, bacterial, or parasitic) within 6 months before randomization. Severe enteric infection is defined as requiring emergency room visit or hospitalization or treatment with antibiotics or anti-infectives due to infection. Nonenteric viral infections, either resolved or well-controlled are not exclusionary.
16. The subject has received any investigational compound within 12 weeks (84 days) or 5 half-lives, whichever is longer, before enrollment into the study.
17. The subject has a contraindication to endoscopy with duodenal biopsy.
    - Contraindication to VCE (strictures, anastomoses, etc) is not an exclusion if the subject is able to complete the other aspects of the study.
18. The subject has additional food allergies (eg, tapioca syrup, oats, almonds, rice crisp, chocolate, almond butter, wheat gluten, cocoa butter, oat flour, glycerin, sunflower lecithin, salt, and natural flavors) to nongluten ingredients in the SIGE bar study food or significant symptoms upon ingestion of the gluten-free SIGE bar during screening.
19. The subject has a history of intolerance, hypersensitivity, or idiosyncratic reaction to an aminoglycoside.
20. Changes or planned changes to the subject's medications or diet that could affect the study between screening and the final visit.
21. The subject has a history of drug or alcohol abuse, or has ongoing use of marijuana during the course of the study, that in the opinion of the investigator, would interfere with the subject's ability to comply with the study requirements.
22. The subject has a known HIV infection or positive tests for hepatitis B or C. The subject has a known clinically significant chronically active hepatopathy of any origin, including cirrhosis, and subjects with persistent positive hepatitis B virus surface antigen and quantitative hepatitis B virus polymerase chain reaction (PCR), or positive serology for hepatitis C virus (HCV) and quantitative HCV PCR within 6 months before the screening visit.
23. The subject is positive for severe acute respiratory syndrome coronavirus 2 at the time of screening and exhibits symptoms that, in the opinion of the investigator, may interfere with study compliance, completion, or accurate assessment of study outcomes or safety (direct

viral or serologic testing may be performed according to site procedures at the discretion of the investigator).

24. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study, during the study, and within 40 days after last dose of the study drug; or intending to donate ova during such time period.
25. If male, the subject intends to donate sperm during the course of this study or within 100 days after the last dose of study drug.
26. Subject has a history or high risk of noncompliance with treatment, study procedures or regular clinic visits.
27. The subject has a known hypersensitivity reaction and/or allergy, including anaphylaxis, to wheat and/or gluten.
28. The subject has a known history of hypersensitivity, idiosyncratic reaction, or intolerance to any ingredients or excipients in TAK-062 and/or placebo.
29. The subject has a current diagnosis of active malignancy or is receiving treatment for active malignancy (hormone therapy alone is not exclusionary). Subjects with fully resected Stage 0 (carcinoma in situ) or Stage 1 tumor without signs of recurrence may participate. All other individuals with malignancies diagnosed in the 5 years prior to screening are excluded.

Region-specific Exclusion Criteria:

30. The subject enrolling in a study in France is not affiliated to a social security scheme or a beneficiary of such a scheme.
31. The subject enrolling in a study in France is deprived of their liberty by a judicial or administrative decision.

7.3 Excluded Medications

All prior and concomitant medications taken within 90 days, including prescription and nonprescription medicines, will be reported in the eCRF beginning at the signing of the informed consent/pediatric assent forms through the final study visit. Subjects will be instructed to avoid all medications listed as exclusions during the entire study.

Subjects must be instructed to avoid:

Digestive enzymes:

- Any over-the-counter digestive enzymes or digestive supplements, other than lactase, including those for gluten digestion. Probiotics are allowable if they were started before screening and not discontinued or changed in dose or type during the study.

Immunosuppressants/immunomodulators: eg, methotrexate, azathioprine, cyclosporine, anti–tumor necrosis factor-α agents, corticosteroids:

- Immunosuppressive doses of corticosteroids: 3 mg per day or more of budesonide for 3 or more consecutive days; more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more, any dose of oral or IV corticosteroids, or high-dose inhaled corticosteroids (>960 µg/day of beclomethasone dipropionate or equivalent), or other systemic immunosuppressive agents.
- Use of drugs that cause villous abnormalities (eg, mycophenolate mofetil, angiotensin receptor blockers, colchicine).

Medications and supplements:

- For treatment of GI symptoms including antiemetics, antidiarrheals, antispasmodics, outside of rescue medications described in Section 7.4. Use of stable doses (ie, more than 4 weeks) of an osmotic, bulking-forming or emollient (surface active agent) laxative is allowed.
- Ongoing chronic use (defined as >7 days continuous use) of a nonsteroidal anti-inflammatory drug aside from <100 mg aspirin, daily, for prophylactic use.

7.4 Rescue Medications

If a subject has symptoms of severe diarrhea, nausea, vomiting, or abdominal spasm that are considered related to their CeD, the use of the medications to treat these severe symptoms will be considered as rescue medications. Instructions for use of all medications (prescriptions and over-the-counter medications), if needed, should be obtained from the study physician. Rescue medication use (dose, date for each occurrence) is to be communicated by the subject to investigator and team, and recorded as concomitant medications as well as an AE. See Appendix G for more information on specific medications, doses, and indications for use of rescue medications.

If these rescue medications are taken 5 out of any 7-day consecutive period or if rescue medications are taken for more than 3 out of a 7-day consecutive period 5 times during the treatment period (after randomization), the subject will be withdrawn from the treatment arm due to lack of efficacy and continued in the study for monitoring and safety.

7.5 Diet

With the exception of the gluten with SIGE bar, subjects must adhere to their prescreening GFD throughout the study. There are no other restrictions on food or fluid intake during the study; however, subjects should not make significant dietary changes during the course of the study.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

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 9.3.16.

Discontinuation of Treatment

1. AE. The subject has experienced an AE, including a liver enzymes and bilirubin abnormalities as noted below, that requires early termination because continued participation imposes an unacceptable risk to the subject's health as per the investigator and/or sponsor criteria, or the subject is unwilling to continue because of the AE.

- Liver enzymes and bilirubin abnormalities.

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.3.11) if the following circumstances occur at any time during study drug treatment:

  – ALT or AST >8 × the ULN, or
  – ALT or AST ≥5 × the ULN and persists for more than 2 weeks, or
  – ALT or AST ≥3 × the ULN in conjunction with elevated total bilirubin >2 × the ULN or international normalized ratio (INR) ≥1.5, or
  – ALT or AST ≥3 × the ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (≥5%).

2. Significant protocol deviation. The discovery postrandomization 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 as per the investigator and/or sponsor criteria.
3. Lack of efficacy. The investigator has determined that the subject has a significant worsening of symptoms and is not benefiting from study treatment and that continued participation would pose an unacceptable risk to the subject or that rescue medications are taken 5 out of any 7-day consecutive period, rescue medications are taken for more than 3 out of a 7-day consecutive period 5 times, or investigator-determined cessation of SIGE administration has lasted more than 2 weeks. The subject will be withdrawn from the treatment due to lack of efficacy and continued in the study for monitoring and safety.

Withdrawal of Subject

4. 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 9.3.14.

5. Lost to follow-up. The subject did not return to the clinic and multiple attempts to contact the subject were unsuccessful. Three attempts to contact the subject must be documented in the subject's source documents.
6. Voluntary withdrawal (withdrawal of consent). The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, must be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).

7. Study termination by sponsor.
8. Other.

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

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject from study drug or study participation treatment at any time during the study when the subject meets the discontinuation or withdrawal criteria described in Section 7.6. 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 due to withdrawal of consent, the primary criterion for discontinuation or termination must be recorded by the investigator. Subjects who discontinue study treatment should be encouraged to have follow-up for the remainder of the study per protocol. In addition, efforts should be made to perform all procedures scheduled for the early termination visit as soon as possible. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to TAK-062 or placebo defined below. TAK-062 active tablets and placebo tablets will be supplied in blister packs and will be labeled with appropriate clinical labels. SIGE bars and gluten-free SIGE bars will be supplied with appropriate clinical labels.

8.1.1.1 TAK-062

TAK-062 is a solid oral dosage form intended for nonsystemic local activity in the stomach. TAK-062 is supplied as [redacted] white to off-white modified capsule-shaped tablet containing

[redacted] TAK-062 enzyme, tableted in its spray-dried form. [redacted]

8.1.1.2 Placebo

The placebo tablet is a white to off-white, modified capsule-shaped tablet containing [redacted]

8.1.1.3 SIGE Bars

The SIGE bars will contain [redacted] (SIGE gluten) or no gluten (gluten-free SIGE). The detailed information on the dosing instructions of the food bars is described in the pharmacy manual. SIGE bars will be provided by the sponsor.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and in the pharmacy manual, and remain in the original container until dispensed. Additional information regarding storage requirements for SIGE bars can be found in the pharmacy manual.

8.1.3 Dose and Regimen

[redacted] Subjects should be instructed that treatment will be effective only for the meal with which it is taken. For this reason, food consumption between meals should be avoided or restricted to unprocessed gluten-free foods.

Subjects will be randomized into study drug and SIGE treatment groups dependent on the enrolling study cohort. The SIGE bars are to be taken with a meal after study drug administration [redacted].

Additional information regarding the dosing instructions for TAK-062 can be found in the pharmacy manual.

Table 8.a describes the dosing regimens for each group in Cohort 1.

Table 8.a Dose and Regimen

Treatment Group	Treatment Description
1	TAK-062 placebo (4 placebo tablets) [redacted] before the start of a meal + SIGE bar with a meal [redacted]: 60 subjects
2	TAK-062 [redacted] (4 TAK-062 tablets) [redacted] before the start of a meal + SIGE bar with a meal [redacted]: 60 subjects

SIGE: simulated inadvertent gluten exposure; [redacted]

Table 8.b describes the dosing regimens for each group in Cohort 2.

Table 8.b Dose and Regimen

Treatment Group	Treatment Description
1	TAK-062 placebo (4 placebo tablets) [redacted] before the start of a meal + SIGE bar with a meal [redacted]: 30 subjects (adults)
2	TAK-062 [redacted] (1 TAK-062 tablet, 3 placebo tablets) [redacted] before the start of a meal + SIGE bar with a meal [redacted]: 50 subjects (adults)
3	TAK-062 [redacted] (2 TAK-062 tablets, 2 placebo tablets) [redacted] before the start of a meal + SIGE bar with a meal [redacted]: 50 subjects (adults)
4 [a]	TAK-062 placebo (4 placebo tablets) [redacted] before the start of a meal + gluten-free SIGE bar with a meal [redacted]: 50 subjects (43 adults, 7 adolescents)
5 [a]	TAK-062 [redacted] (4 TAK-062 tablets) [redacted] before the start of a meal + gluten-free SIGE bar with a meal [redacted]: 50 subjects (43 adults, 7 adolescents)
6 [a]	TAK-062 [redacted] (1 TAK-062 tablet, 3 placebo tablets) [redacted] before the start of a meal + gluten-free SIGE bar [redacted]: 7 subjects (adolescents only)

SIGE: simulated inadvertent gluten exposure; [redacted].

[a] Adolescent subjects will be randomized to Groups 4, 5, and 6 only.

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 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, to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are considered as AEs and should be captured with the appropriate Preferred Term of overdose in the AE eCRF. Additionally, AEs associated with an overdose will be documented on AE eCRF(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 a drug overdose, the subject should be treated according to the standard practices of the Investigator and the site.

There is no experience with overdose with any of TAK-062 formulations.

8.2 Study Drug and SIGE Assignment and Dispensing Procedures

After confirming a subject meets all entry criteria, the investigator or the investigator's designee will access the interactive response technology (IRT) to enroll the subject into [redacted] and then randomize the subject into the study at Visit 3. The identification (ID) numbers of the study drug and SIGE bars to be dispensed will be provided by the IRT.

On occasion in unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic, additional drug supply may be provided to subjects (either at an in-person visit or delivered to subject's residence) to cover extended periods between on-site visits. Any additional re-supply must be reviewed and approved in advance by the sponsor or designee.

If sponsor-supplied drug or SIGE bars are lost or damaged, the site can request a replacement from IRT. (Refer to IRT manual instructions provided separately.) The investigator or designee will again access IRT to request additional study drug and SIGE bars for a subject.

Sites should follow the instructions provided in the pharmacy manual to send study drug and/or SIGE bars to subjects at home when an onsite visit for dispensation is not feasible.

8.3 Randomization Code Creation and Storage

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

8.4 Study Drug and SIGE Blind Maintenance

The study drug and SIGE blind will be maintained using the IRT.

Subjects, site staff, and study team members will remain blinded to treatment assignment, individual subject ADA, GIP, and PK data from this study until database lock occurs for this study. In the event that results must be reported to the investigator before breaking the blind, all efforts should be made to maintain the blind. Subjects, site staff, and study team members involved in study operations on an everyday basis will also remain blinded to postrandomization histology.

8.5 Unblinding Procedure

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

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

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study but should be followed up for safety purposes.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs and SIGE Bars

The investigator or designee must ensure that the sponsor-supplied drug/SIGE bar 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/SIGE bar, the investigator or designee must maintain records of all sponsor-supplied drug/SIGE bar 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/SIGE bar, 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 recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the medication ID dispensed.
- Verifying that all containers used 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/SIGE bar is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs/SIGE bars on a sponsor-approved drug/SIGE bar 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/SIGE bar and amount dispensed including initials, seal, or signature of the person dispensing the drug/SIGE bar, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person

receiving the sponsor-supplied drug/SIGE bar. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug/SIGE bar is dispensed.

All study drug/SIGE bar not returned to the site by a subject must be investigated by the site and appropriately documented on the drug/SIGE bar accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug/SIGE bar accountability and reconciliation before sponsor-supplied drugs/SIGE bar are returned to the sponsor or its designee for destruction or destroyed at the site. Accountability for clinical study material being destroyed at the site must be documented using a study accountability tracking document or equivalent document. In addition, a certificate of destruction document or equivalent must be provided by the sites that can identify or allow traceability to the batches, and/or medication ID numbers involved, and actual quantities destroyed. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug/SIGE bar accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

In the event of expiry date extension of sponsor-supplied drug/SIGE bar already at the study site, sponsor-supplied drugs/SIGE bar may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

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.

9.2 Administrative Procedures

9.2.1 Informed Consent/Pediatric Assent Procedure

The requirements of the informed consent/pediatric assent are described in Section 15.3.

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

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

9.2.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age at time of informed consent/pediatric assent, sex, Hispanic 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 relevant to the disease under study that resolved at or before signing of informed consent/pediatric assent forms.

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/pediatric assent forms.

9.3 Clinical Procedures and Assessments

9.3.1 Physical Examination Procedure

A baseline physical examination (defined as the assessment performed during Visit 1) 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; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment before first dose examination. Clinically significant findings in physical examination will be entered as AEs in the eCRF.

9.3.2 Weight, Height, and BMI

A subject should have weight and height measured following standard measuring procedures. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI will be derived as:

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

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

9.3.3 Vital Sign Procedure

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

9.3.4 ECG Procedure

A standard 12-lead ECG will be recorded and interpreted locally by the investigator (or a qualified observer at the study site) using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

9.3.5 GFD Knowledge Quiz

Potential subjects must complete a knowledge test of what foods are and are not permitted in the GFD. This knowledge test is based on the scale developed by Silvester et al (Silvester et al. 2016). It consists of 3 fill-in-the-blanks as to which grains are to be avoided (wheat, barley, rye),

4 true/false questions and 10 foods to assess as “allowed” “to question” or “not allowed”. All completed GFD knowledge quizzes are to be retained on site as source. The final determination of adequate comprehension of a GFD is at the discretion of the investigator.

9.3.6 PRO Assessments

The schedule of administration of the following PRO assessments can be found in Schedule of Study Procedures (Appendix A). All PROs will be administered on an electronic device. The CDSD and supplemental frequency questionnaire will be administered at approximately the same time every day. All PROs should be done, before any other procedures on the day of the study visit or no more than 1 day before the study visit and in the following order:

1. EQ-5D-5L.
2. PGIS.
3. PGIC.
4. CeD Most Bothersome Symptom.
5. PROMIS—Fatigue Instrument.
6. CeD-GSRS.
7. PROMIS—Cognitive Function Instrument.
8. WPAI+CIQ:CeD.
9. SF-12 v2.
10. ICDSQ.
11. CDAQ.
12. CD-QoL.

9.3.6.1 CDSD v2.1

The CDSD v2.1 is a 5-item, self-administered questionnaire that evaluates the severity of CeD symptoms on a daily basis. Severity is measured for the following CeD symptoms: diarrhea, abdominal pain, bloating, nausea, and tiredness. Symptom severity is evaluated using 5-point Likert-type scales (none, mild, moderate, severe, and very severe). A supplemental questionnaire administered with the CDSD will measure the frequency of bowel movements, vomiting, and diarrhea.

9.3.6.2 EQ-5D-5L

The EQ-5D-5L questionnaire, developed by the EuroQol Research Foundation is a simple, valid, and reliable instrument used to measure general health-related quality of life (HRQOL) in subjects and includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Within each dimension, subjects choose 1 of 5 levels of health problems (none, slight, moderate, severe, or extreme), with levels scored 1 through 5, respectively. The

EQ-5D-5L visual analog score is a self-assigned rating of overall health using a visual, vertical scale, with a score of 0 as the worst and 100 as best possible health. The EQ-5D-5L total score and EQ-5D-5L visual analog score have been shown in many studies to be valid and reliable instruments for measuring HRQOL in subjects with GI diseases (Herdman et al. 2011).

9.3.6.3 PGIS

PGIS is a 1-question instrument used as an anchor that evaluates the overall severity over the past 7 days. Response options are measured using a Likert-type scale (no symptoms, mild, moderate, severe, very severe). For validation purposes, it will be performed at Weeks -8 and -7. The PGIS will also be conducted on the day of every visit.

9.3.6.4 PGIC

The CeD PGIC is a 1-question instrument that evaluates the change from study start to the present time. Response options are measured using a 7-point Likert-type scale (very much worse, much worse, a little worse, no change, a little improved, much improved, very much improved).

9.3.6.5 CeD Most Bothersome Symptom

The CeD Most Bothersome Symptom is a 1-question instrument designed to assess the subject's perception of which symptoms from those evaluated in the CDSD that the subject considers most bothersome.

9.3.6.6 PROMIS—Fatigue Instrument

PROMIS is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. The PROMIS Item Bank v1.0—Fatigue—Short Form 13a (2019b) is a battery of 13 questions for adults aged 18 years or older, which are included in the FACIT-Fatigue. This instrument assesses a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities. This instrument has a 7-day recall period, and responses are measured using a 5-point scale (not at all, a little, somewhat, quite a bit, very much). For subjects aged 12 to 17 years, the PROMIS Pediatric Item Bank v2.0—Fatigue—Short Form 10a: Pediatric Fatigue will be used. This instrument has 10 questions with a 7-day recall that are measured using a 5-point scale (never, almost never, sometimes, often, almost always).

9.3.6.7 CeD-GSRS

The GSRS is a nondisease-specific 15-item instrument measuring the discomfort of GI symptoms using a modified Likert scale (no discomfort at all, minor discomfort, mild discomfort, moderate discomfort, moderately severe discomfort, severe discomfort, very severe discomfort) (Revicki et al. 1998). In this study, the 10 items relevant to CeD (CeD-GSRS) will

be evaluated (stomach pain/discomfort, hunger pains, nausea, rumbling in stomach, bloating, burping, passing gas, diarrhea, loose stools, urgent bowel movement) (Leffler et al. 2012).

9.3.6.8 PROMIS—Cognitive Function Instrument

PROMIS is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. The PROMIS Short Form v2.0—Cognitive Function 6a (2019a) is a subset of 6 items assessing patient-perceived cognitive deficits. Facets include mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes in these cognitive functions. The extent to which cognitive impairments interfere with daily functioning, whether other people observe cognitive impairments, and the impact of cognitive dysfunction on quality of life are also assessed. This instrument has a 7-day recall period, and responses are measured using a 5-point frequency scale (never, rarely, sometimes, often, very often). For subjects aged 12 to 17 years, a modified version of the PROMIS Pediatric Short Form v1.0—Cognitive Function 7a: Pediatric Cognitive Function will be used. This instrument has 7 items on a 5-point response scale (none of the time, a little of the time, some of the time, most of the time, all of the time). The original version has a 4-week recall that has been modified to 7 days.

9.3.6.9 WPAI+CIQ:CeD

The WPAI+CIQ:CeD (Reilly et al. 2004) is a 10-question instrument questionnaire. The questionnaire assesses work time or academic classes lost due to CeD. Subjects also self-assess the impact of allergies on the performance in the workplace, at school, or during university classes. The recall period is the previous 7 days.

9.3.6.10 SF-12 v2

The SF-12 v2 is a self-administered, validated questionnaire designed to measure generic HRQOL (Ware et al. 2001). This 12-item questionnaire measures 8 domains, including: Physical Functioning, Role-physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-emotional, and Mental Health. Two summary scores can be calculated, the Physical Component Score, and the Mental Component Score. Higher scores indicate better health status.

9.3.6.11 ICDSQ

The ICDSQ is a 14-question instrument that evaluates emotional wellbeing, physical functioning, social activities, and daily activities over the past 7 days. Responses are measured using a 5-point Likert-type scale (not at all, a little, moderately, very much, completely).

9.3.6.12 CDAQ

The CDAQ (Crocker et al. 2018) is a validated PRO measure developed to investigate the HRQOL of people living with CeD with a recall period of 4 weeks. This 32-item questionnaire measures 5 domains: stigma, dietary burden, symptoms, social isolation, and worries and concerns. Responses are measured using a 5-point Likert-type scale (never, rarely, sometimes, often, always).

9.3.6.13 CD-QoL

The CD-QoL (Dorn et al. 2010) is a 20-item questionnaire measuring the quality of life in celiac patients over a 30-day time period. Responses are measured on a 5-point Likert-type scale (not at all, a little, moderately, very much, completely).

9.3.7 Placebo Reduction Plan

9.3.7.1 Accurate Symptom Reporting Training

The Accurate Symptom Reporting training is an electronic learning module designed to orient subjects to core study questionnaires and to provide guidance on how to report symptoms accurately and reliably. The goal of this training is to improve the accuracy of PRO data. Once training is available, subjects may receive training at Visits 1, 2, and 3, as well as at Weeks 6, 10, 16, and 22. Additional training may be performed on an as needed basis.

9.3.7.2 Placebo Response Reduction Training

The placebo response reduction training teaches the subject about the appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide subjects with truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies. Once training is available, subjects may receive training at Visits 1, 2, and 3, as well as at Weeks 6, 10, 16, and 22. Additional training may be performed on an as needed basis.

9.3.7.3 Participant Scorecard

The Participant Scorecard presents subjects with data reflecting their own performance on key tasks in the study, plus automated and customized tips for how to improve their performance. Scores are assigned for eDiary compliance, study medication adherence, and SIGE bar adherence, providing subjects with the opportunity to make changes to improve their performance on these tasks if needed. The Scorecard was designed to be viewed without any required human intervention in order to improve efficiency and timeliness of recommendations and decrease biases and burdens introduced by filtering retraining through site staff.

9.3.7.4 Research Subject Responsibilities Training

The Research Subject Responsibilities training is an electronic learning module designed to provide a detailed overview of the key study procedures (eg, dosing, SIGE bar, diary completion) to the subjects. Once training is available, subjects will receive training at Visits 1, 2, and 3, as well as at Weeks 6, 10, 16, and 22. Additional training may be performed on an as needed basis.

9.3.8 Exit Interview – United States Only

The objective of the exit interview is to supplement, support, and facilitate the interpretation of data from the PRO and clinical measures. Exit interviews will be conducted by an independent

party with a subset of subjects who enrolled in the study from selected sites, with competitive enrollment. Only consented subjects and sites will be invited to participate in exit interviews. Interviews will be scheduled within 10 days of Week 24 (Visit 6) or early termination. The contents of the interview will include the following topics:

- Disease-related symptoms before the study and their bothersomeness ratings.
- Impact of disease on subjects' lives before starting the clinical study.
- Experiences with study treatment.
- Anticipated or unanticipated benefits of treatment, impact of those benefits.
  - Impact of treatment on daily life/functioning.
  - Impact of treatment on most important/bothersome symptoms.
- Importance or meaningfulness of perceived benefits of treatment.
  - Symptom-free days.
  - Minimal symptom days.
- How well treatment addresses most important/bothersome symptoms.
- Onset of benefits/changes.
- Treatment experiences.
- Satisfaction levels with treatment and reasons for satisfaction.

9.3.9 Endoscopy and Biopsy Collection

An upper GI endoscopy and duodenal biopsy will be performed by qualified and experienced endoscopists. Standard procedures will be followed for conscious sedation, gastroduodenoscopy, and biopsy. Screening biopsy specimens must be taken and provided to the central pathology laboratory approximately 4 weeks before the planned baseline visit to allow sufficient time for processing and central review and determination of eligibility. At the time of the endoscopy, sigmoidoscopy with biopsy may be performed (at the discretion of the investigator) to rule out microscopic colitis in subjects who qualify for study inclusion based on diarrhea severity and who have not had previous sigmoidoscopy or colonoscopy with biopsies providing evidence of lack of microscopic colitis. The upper GI endoscopy will be performed at Week -4 (Visit 2) and at Week 24 (Visit 6) or early termination. All possibly significant macroscopic abnormalities in the esophagus, stomach, duodenal bulb, and descending duodenum will be documented in the eCRF. A minimum of 6 and up to 8 small bowel biopsy specimens will be taken from separate folds/circumferential areas of the distal (postbulbar, D2/D3) duodenum. Samples will be collected and placed into formalin for Vh:Cd, IEL, and other exploratory analyses or snap frozen and potentially used for microbiome or other exploratory analyses related to GI immunology. Hematoxylin and eosin stained slides from small bowel biopsy specimens will be used to perform quantitative and qualitative morphometric analysis, which includes measurement of Vh and Cd and calculation of their ratio (Vh:Cd).

Biopsies should be taken with standard biopsy forceps with 1 biopsy taken per pass and placed into separate specimen vials. Additional biopsies should not be taken for assessment at the local laboratory unless deemed necessary for subject safety in the setting of an incidental finding.

Additional instructions will be provided in a central pathology laboratory manual.

At the central histopathology core laboratory, the histological efficacy assessment will be performed using the formalin-fixed, paraffin-embedded specimens. Morphometric analysis of the small bowel biopsy specimens involves measurement of Vh and Cd and calculation of their ratios (Vh:Cd). The Vh and Cd measurements will be obtained from well oriented biopsy samples as previously described (Adelman et al. 2018; Taavela et al. 2013) and across multiple loci so as not to miss patchy forms of villous atrophy. Staining of the samples for CD3 will also be used for quantitation of CD3+ IEL density numbers in the tissue.

9.3.10 [redacted]

[redacted]

9.3.11 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.

Direct viral or serologic testing for COVID-19 may be performed according to site's standard of care and at the discretion of the investigator.

Table 9.a lists the tests that will be obtained for each laboratory specimen, as well as additional tests and various time points.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	ALT	Albumin
WBC including differential	Albumin	Protein
Hemoglobin	ALP	Glucose
Hematocrit	AST	pH
Platelets	Total bilirubin	Leukocytes
HbA1c	Total protein	Blood
	Creatinine	Bilirubin
	Blood urea nitrogen	Urobilinogen
	Creatine kinase	Ketone
	GGT	Creatinine
	Potassium	
	Sodium	

Other:

Celiac serologies:	
IgA-tTg	
DGP	
Serum	**Urine**
CRP	hCG [a] (for pregnancy)
Beta hCG [a] (for pregnancy)	GIP
FSH (if menopause is suspected)	
HIV test	
Hepatitis B and C	
ADA	

ADA: antidrug antibody; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; DGP: deaminated gliadin peptide; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; GIP: gluten immunogenic peptide; HbA1c: glycosylated hemoglobin; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; Ig: immunoglobulin; RBC: red blood cell; tTg: tissue transglutaminase; WBC: white blood cell.

[a] For female subjects of childbearing potential only.

Test for international normalized ratio should be performed locally for elevated liver enzyme and bilirubin evaluation.

The central laboratory will perform laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

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 within 24 hours. Hepatic investigations as suggested in Table F-1 of Appendix F 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. (Refer to

Section 7.6 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver enzymes and bilirubin.)

If ALT or AST is elevated ≥3 × ULN or the total bilirubin is elevated ≥2 × ULN, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3).

Abnormal laboratory tests at screening may be retested at the investigator's discretion (see Section 9.3.16).

9.3.12 PK and Biomarker Sample Collection and Analysis

9.3.12.1 Collection of Blood and Plasma for PK Sampling

Blood samples to evaluate the PK of TAK-062 in plasma will be collected at Weeks -4, 0, 3, 12, 24, and 28 as specified in Appendix B. Approximately 10 adult subjects enrolled in Cohort 1 and 30 adults subjects enrolled in Cohort 2 will participate in PK subgroup for a slightly more intensive collections at Week 0 (randomization) and Week 3 visits, including predose and 0.5, 1, 2, 3, and 4 hours (optional) postdose collections. All other subjects will be required to provide PK samples at predose, 0.5, and 1 hours postdose with additional collections as optional at these 2 visits. At Week 12, all subjects will be required to provide PK samples at predose, 0.5, and 1 hours postdose with additional collections as optional. At Week -4, 24, and 28 visits, PK samples will be collected at any time during the visit.

The actual date and time of the sample collections, as well as the date and time for the current dose and the most recent dose before visit, should be accurately recorded in the eCRF. When predose samples are scheduled, subjects should be instructed to bring their scheduled dose of study drug to the clinic with them so the predose sample can be collected before the study drug is taken. PK samples should be collected as follows: predose sample (up to 30 minutes prior to dosing), postdose samples at 0.5 hr (±5 minutes), 1 hr (±10 minutes), 2 hr (±10 minutes), 3 hr (±15 minutes), and 4 hr (±15 minutes). While all efforts should be made to obtain the PK samples at the scheduled nominal time (or within the designated time frame specified in Schedule of Study Procedures [Appendix A]), collections outside of the allowed time window may not be considered a protocol deviation if the actual collection time as well as date and time of dosing are accurately captured.

Collected samples will be stored for batch analysis of TAK-062 using a validated analytical method. Detailed instruction for handling, processing, storing, and shipping of plasma samples are provided in the laboratory manual.

9.3.12.2 Biomarker Collection

Tissue samples to evaluate IELs, Vh:Cd ratio, other qualitative and quantitative histology endpoints, RNA, and microbiome will be collected through duodenal biopsies as noted in Schedule of Study Procedures (Appendix A). Urine samples will be collected to monitor GIP qualitatively and quantitatively as noted in Schedule of Study Procedures (Appendix A). Predose

plasma and serum samples will be collected as noted in the Schedule of Study Procedures (Appendix A).

9.3.13 Contraception and Pregnancy Avoidance Procedure

9.3.13.1 Male Subjects and Their Female Partners

From the time of signing of informed consent/pediatric assent forms, 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 an effective contraception in combination with their female partner using an effective method of contraception, as below. In addition, they must be advised not to donate sperm during this period. WOCBP who are partners of male subjects are also advised to use additional contraception as shown in the list containing effective contraception below.

9.3.13.2 Female Subjects and Their Male Partners

From the time of signing of informed consent/pediatric assent forms, throughout the duration of the study, and for 40 days after last dose of study drug, WOCBP* who are sexually active with a nonsterilized male partner** must use an effective method of contraception from the list below.

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

9.3.13.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

*A woman is considered a WOCBP that is, fertile, following menarche and until becoming postmenopausal 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 men should be at least 1-year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

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

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**	**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] – Oral. – Intravaginal. – Transdermal. • Progestogen only hormonal contraception associated with inhibition of ovulation. – Oral. – Injectable. • Sexual abstinence. [b] • Refraining from donating sperm. [c]	• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide. [f] • Cap, diaphragm or sponge with spermicide. [f] • Combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods).
Low User Dependency	
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation. [a] • IUD. • IUS. • Bilateral tubal occlusion. • Vasectomy; vasectomized partner. [d, e]	
Measures Intended to Prevent Fetal and Neonatal Exposure via Sperm or Breastmilk	
• Participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration 40 days after the last dose. • Participants 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] 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 participant.

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

[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.

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	Effective Contraceptives Failure rate of >1% per year when used consistently and correctly

[e] For participants of childbearing ability, having a vasectomized partner is a highly effective contraception method provided that the partner is the participant'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] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

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 amenorrhoea method (LAM).

Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent/pediatric assent 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 WOCBP and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- Assessment of subject compliance through questions such as
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - 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),

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.

9.3.14 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn from the study and any sponsor-supplied study 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 study drug, eg, after the randomization visit, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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

9.3.15 Documentation of Concomitant Medications

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

9.3.16 Documentation of Screen Failure

Investigators must account for all subjects who sign an informed consent/pediatric assent forms.

If the subject does not meet eligibility criteria following completion of screening assessments, the investigator should complete the eCRF. The investigator or designee will document the subject as a screen failure in IRT.

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

- Pretreatment event (PTE)/AE.
- Screen failure (did not meet inclusion criteria or exclusion criteria).
- Lost to follow-up.
- Withdrawal by subject.
- Study termination by sponsor.

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

Subjects who do not meet all inclusion criteria or meet an exclusion criteria and have not been randomized are considered screen failures may undergo rescreening once after discussion with the medical monitor. Rescreening will not be permitted for subjects who screen fail due to Vh:Cd >2.5 or negative HLA testing. A rescreened subject will receive a new ID number. A subject can be re-screened 1 time.

If a subject is rescreened, all screening tests will be repeated except the following:

- HLA testing.
- Hepatitis and HIV testing if it occurred within 3 months before the initial rescreening visit.

9.3.17 Documentation of 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 screen failure on the applicable eCRF.

Randomization will be stratified by celiac serologic status at Visit 1, defined as normal or elevated celiac serology (1 or more of the following: IgA-tTg >1 × ULN, IgA-DGP >2 × ULN, or IgG-DGP >2 × ULN), mild to moderate (Vh:Cd 1.5 to <2.5) versus moderate to severe (Vh:Cd <1.5) histologic injury at baseline, and by the use of PPIs or histamine type 2 receptor antagonists (yes or no) at Visit 1.

9.4 Monitoring Subject Treatment Compliance

Subjects will be required to return study drug containers/unused study drugs to the site.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records. Subjects will be instructed to complete a daily diary and the site will monitor compliance of study drug and SIGE bar.

9.5 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).

Each evening, subjects will complete their daily diary electronically.

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 (Appendix A), investigators may consult with the medical monitor to continue subjects in the study despite departure from the Schedule of Study Procedures (Appendix A). Investigators are expected to evaluate the impact to the safety of the study subjects and site personnel for subjects to continue.

When a scheduled visit is not conducted in-person, site staff will speak directly with the subject by telephone or other medium where acceptable (eg, a computer-based video communication) during the visit window to assess subject safety and overall clinical status. During this contact, the study site physician or other qualified site staff should also, at a minimum, conduct the following assessments: ask about any information on AE reported by subject since last visit, this should be collected, as well as concomitant medication documentation. Other study assessments may be collected remotely as is feasible, and may involve audio or video recording if allowed per local, state, or country regulations. Additionally, sites may send staff or send home health care as contracted by the sponsor to subjects to conduct study assessments contingent upon local regulations.

9.6 Biological Sample Retention and Destruction

The samples will be sent to a central laboratory that processes the blood, urine, and tissue samples and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely for up to 15 years or less according to local regulations with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

When subjects request disposal of a stored sample during the retention period, the site will ask the central laboratory or sponsor-approved vendor to destroy the sample via the sponsor according to the procedure. The central laboratory or sponsor-approved vendor will destroy the sample in accordance with the procedure and notify the site and sponsor.

Subjects who consented and provided biomarker samples for analysis can withdraw their consent and request disposal of a stored sample at any time.

The sponsor has put into place a system to protect the subject's personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

9.6.1 Flexible Options for Study Procedures in Response to Pandemic

The following information provides guidance regarding flexibility to perform study procedures that could be implemented for study subjects or study sites during the course of this study in response to a pandemic or the lasting effects of a pandemic (eg, COVID-19 or other future

similar unexpected public health concerns) that require physical distancing that may result in subjects missing their visits.

Optional flexible measures include the following:

- Informed consent/pediatric assent forms procedure: If necessary, informed consent/pediatric assent from a potential or current study subject may be obtained via electronic informed consent/pediatric assent capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site, based on local regulations or requirements.
- Clinical laboratory samples: Blood draws may be conducted at home by study authorized personnel or a local laboratory (or relevant clinical or office facility) authorized/certified to perform such tests routinely.
- ECG procedures: ECGs may be performed during a home health care visit by a qualified health care professional who is authorized/certified to perform such tests routinely.
- Vital signs: Vital sign measurements may be performed during a home health care visit by a qualified health care professional who is authorized/certified to perform such tests routinely.
- Physical examination: Examinations may be conducted as a nurse assessment or via telehealth visit, per investigator's discretion, during home health care visits, if applicable, and according to local regulations/requirements.

10.0 PTEs AND AEs

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent/pediatric assent forms) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, x-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

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

Worsening of PTEs or AEs:

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

Changes in intensity of AEs/serious PTEs:

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

AEs related to gluten exposure

- AEs related to gluten may be anticipated to include signs and/or symptoms of CeD, including GI symptoms and extraintestinal manifestations such as skin rash, headache, fatigue neurological/neurocognitive manifestations, elevation in liver enzymes and bilirubin, and joint pain. Symptoms collected through the CDSD, 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 (see Section 7.4) and/or become SAEs. If severe symptoms require use of rescue medications, each episode of rescue medication use is considered as an AE.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent/pediatric assent forms are not considered PTEs or AEs. However, if a preplanned procedure is performed early ie, after subject has started study drug (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs if these events occur after subject has commenced study drug.

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

- All cases of overdose (with or without associated AEs) will be documented in the dosing section of the eCRF. Additionally, overdose should be captured as an AE in the eCRF with or without any additional AEs.

  An overdose will be considered as a dose above the maximum recommended dose that is being used in this study irrespective of the assigned study arm of the subject that overdosed. Any administered dose above that assigned to the subject that is less than the maximum dose being studied will be considered as a medication dosing error, and not an overdose.

[redacted] endoscopy procedure related AEs:

- Any incidental safety findings from local reading of the [redacted] or during the baseline endoscopy procedure may be considered as a PTE for the study; however, before this is captured as PTE, the site must consult with sponsor's study physician as the decisions will be made on a case by case basis.
- These incidental safety findings will be tracked in subsequent [redacted]/endoscopy visits and any changes observed from baseline findings may be captured as TEAEs after discussing with sponsor's study physician.

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

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 AEs of Special Interest

There are no AEs of special interest for TAK-062.

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

Liver AEs will be characterized per FDA guidelines (Appendix F).

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 underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs. Relationship to SIGE will be assessed and recorded separately from other study procedures.

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 on which the subject recovered, the AE resolved but with sequelae or the subject died.

10.1.11 Pattern

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. Other events occur once or 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 any dose modification and/or stopping a study drug.
- Unknown: only to be used if it has not been possible to determine what action has been taken.
- Not applicable: a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose interrupted: the dose schedule was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/resolved: Subject returned to baseline assessment status with respect to the AE/PTE.
- Recovering/resolving the intensity is lowered by 1 or more grades: 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 another cause with the particular AE/PTE state 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 gotten worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae: the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: the AEs/PTEs which are considered as the cause of death.
- Unknown: the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent/pediatric assent forms to participate in the study and continue until just before the subject is first administered study drug (Visit 3) 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). Routine collection of AEs will continue until 30 days after the administration of the last dose of study drug.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. 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 such as 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 AE is related to the study drug treatment. The following information will be documented for each AE:

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

9. Seriousness.

All PROs 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 the instruments, 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 followed.

10.2.2 Collection and Reporting of SAEs

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

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

- A short description of the AE and the reason why the AE is categorized as serious.
- Subject ID number.
- Investigator's name.
- Name of the study drug.
- 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 Enzymes and Bilirubin

For any subject with ALT ≥3 × ULN ***AND*** total bilirubin >2 × ULN ***OR*** INR >1.5 for which an alternative etiology has not been found, report the event as an SAE, contact the sponsor's medical monitor within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix F.

Other Grade 3 or 4 laboratory abnormalities (per CTCAE v5.0) should be assessed for clinical significance by the investigator or qualified subinvestigator. Clinically significant laboratory abnormalities should be confirmed by repeat testing and the medical monitor should be contacted.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date (after the last dose), the investigator should complete a follow-up SAE form or provide other written

documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is being conducted. Relative to the first awareness of the AE 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, and 15 days for other SAEs, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety concerns 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 trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 IDMC

According to ICH E6 (1.25) an IDMC (eg, Data and Safety Monitoring Committee, Monitoring Committee, Data Monitoring Committee) may be established by the sponsor to assess at intervals the progress of the study, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a study.

The minimal description of the IDMC should include:

- Composition (number of members and expertise).
- Frequency of meetings/assessments.
- Purpose and authority.
- Scope of data review.

Details of the IDMC roles and responsibilities are captured in the IDMC charter prior to the start of the trial.

An external IDMC is warranted to ensure the drug is safe and efficacious in adults before dosing in adolescents.

The primary responsibility of the IDMC is to safeguard study subjects, in particular the adolescent subjects, by reviewing and assessing the clinical safety data being collected during the

performance of the study. The IDMC will review SAEs and AEs ≥Grade 3. The IDMC will also meet periodically throughout the study to review cumulative safety data. Based on these data evaluations, the IDMC will make recommendations to the sponsor to continue the study as planned, or to modify, temporarily suspend, or terminate the treatment group or study. The IDMC will be responsible for identifying issues and making recommendations regarding the monitoring of the subjects for safety, including the collection of additional safety data. IDMC will also be reviewing IA data and notifying the sponsor of the recommendation to include adolescent group. The sponsor will be responsible for notifying investigators and regulatory authorities of any IDMC recommendations, as appropriate.

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 latest 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 informed consent/pediatric assent forms.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff on 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.

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

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

12.2 Record Retention

The 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 ID log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent/pediatric assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent/pediatric assent forms), 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, 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.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before any unblinding of study data for the IA. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before unblinding of subject's 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

Full analysis set (FAS)–SIGE: All randomized subjects who are randomized to receive gluten-containing SIGE.

FAS–no SIGE: All randomized subjects who are randomized to gluten-free SIGE.

Safety analysis set (SAF): All randomized subjects who received at least 1 dose of study drug.

SAF-SIGE: All randomized subjects who received at least 1 dose of study drug and gluten-containing SIGE.

SAF–no SIGE: All randomized subjects who received at least 1 dose of study drug and gluten-free SIGE.

Per-protocol set (PPS)–SIGE: All subjects in FAS-SIGE who do not violate the terms of the protocol in a way that would impact the study outcome. All decisions to exclude subjects for the PPS will be made before the unblinding of the study.

The PK analysis set: All randomized subjects who received at least 1 dose of study drug with at least 1 measured PK concentration.

Immunogenicity analysis set: All randomized subjects who received any TAK-062 and have the baseline and at least 1 postbaseline immunogenicity sample assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics including stratification factors will be presented by treatment group and overall for FAS-SIGE and FAS–no SIGE. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, race). Individual subject demographic and baseline characteristics data will be listed.

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).

13.1.3 Efficacy Analysis

All efficacy analyses for the treatment period will be conducted using the FAS-SIGE and FAS–no SIGE separately. All statistical hypothesis testing will be 2-sided using a significance level of 0.05 unless otherwise stated. Baseline value will be defined as the most recent nonmissing results before the first dose of study treatment unless otherwise specified. The placebo group for analyses based on FAS-SIGE will include all subjects randomized to receive placebo [redacted] and gluten-containing SIGE bars [redacted] from Cohorts 1 and 2 unless specified otherwise.

13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12

The primary efficacy analysis will be based on FAS-SIGE. The weekly CDSD GI symptom severity score is an average of the daily GI symptom severity scores during the week. The daily GI symptom severity score is the average of the severity score for diarrhea, abdominal pain, bloating and nausea, ranging from 0 (no symptoms) to 4 (very severe). Weekly CDSD scores will be calculated where the CDSD is completed on at least 4 of the 7 days. When the daily diary is completed on less than 4 of the 7 days, the weekly CDSD GI symptom severity score will be considered missing in the primary analysis. The attributes of the primary estimand are:

- Population: Subjects with clinically active CeD and small intestinal villous atrophy who are experiencing inadvertent gluten exposure and meet all the eligibility criteria.

- Variable/endpoint: Change in weekly CDSD GI symptom severity score from baseline to Week 12.
- Treatments: TAK-062 ([redacted]) versus placebo.
- Intercurrent events (ICEs): Treatment discontinuation (due to AE or other reasons), SIGE bar discontinuations, and use of rescue medications for CeD symptoms.
  - Strategy for addressing ICEs: A composite strategy will be used to address rescue medication use and treatment discontinuation due to lack of efficacy or treatment-related AEs. For subjects who use rescue medications for CeD-related symptoms, the severity of the treated GI symptom(s) in CDSD on the days when the rescue medications are used will be set to very severe. For subjects who discontinue treatment due to lack of efficacy or treatment-related AEs, the Week 12 CDSD severity score will be set to the baseline (Week -1) weekly CDSD GI symptom severity score. A treatment policy strategy will be used to address SIGE bar discontinuation (ie, the recorded weekly CDSD GI symptom severity score will be used regardless of whether a subject has discontinued SIGE) and treatment discontinuation due to reasons other than lack of efficacy or treatment-related AEs.
- Population-level summary: Treatment difference (TAK-062 – placebo) in the mean change from baseline to Week 12 in weekly CDSD GI symptom severity score, for each dose level.

The primary endpoint will be analyzed with a mixed model for repeated measures (MMRM) approach using the appropriate contrast at Week 12. The model will be based on all available weekly CDSD GI symptom severity scores from Week -1 through Week 12. The model will include treatment group, week, treatment-by-week interaction, and the randomization stratification factors as fixed effects and baseline CDSD GI symptom severity score as covariates. An unstructured covariance structure will be used to model the within-subject errors. If the model does not converge, additional covariance structure will be used with the order specified in the SAP. Two-sided tests comparing each of the TAK-062 dose groups with placebo at Week 12 will be conducted. The corresponding p-values, LS means of treatment differences and 2-sided 95% CI will be reported. The MMRM assumes data is missing at random. Sensitivity analysis will be performed with alternative assumption that data is missing not at random.

Multiplicity control: To control the overall type I error rate for the primary endpoint, a fixed-sequence testing procedure will be used for the comparison of 3 doses of TAK-062 versus placebo. Specifically, the primary endpoint tested will be conducted in the following order:

i. First, [redacted] TAK-062 versus placebo for subjects taking gluten-containing SIGE.
ii. If the test in Step 1 is statistically significant, then perform the superiority test of [redacted] TAK-062 versus placebo for subjects taking gluten-containing SIGE.
iii. If the test in Step 2 is statistically significant, then perform the superiority test of [redacted] TAK-062 versus placebo for subjects taking gluten-containing SIGE.

Supplementary analyses for the primary estimand will include the following:

- Estimand with the target population of subjects who satisfied study entry criteria and are on pre-enrollment diet. The primary endpoint will be analyzed based on FAS–no SIGE. The endpoint, strategy for the ICEs and population-level summary will be the same as the main estimand. Nominal p-values will be calculated. No hypothesis testing will be performed.
- Estimand with the target population excluding subjects who report >1 point improvement in PGIS during [redacted] run-in period. The supplementary analysis will be performed for FAS-SIGE and FAS–no SIGE separately. The endpoint definition, strategy for the ICEs and population-level summary will be the same as the main estimand. Nominal p-values will be calculated. No hypothesis testing will be performed.
- Estimand with the weekly CDSD-overall (GI + Tiredness) symptom severity score based on daily CDSD symptom severity score that is the average of the severity score for diarrhea, abdominal pain, bloating, nausea, and tiredness, ranging from 0 to 4. The population, treatments, strategy for the ICEs and population-level summary will be the same as the main estimand. The analysis will be performed based on FAS-SIGE and FAS–no SIGE separately. Nominal p-values will be calculated. No hypothesis testing will be performed.
- Estimands using the area under the curve (AUC) of daily CDSD GI symptom severity score from Day 1 through Week 12 as the endpoint. The AUC will be a summation of daily scores. Missing values due to study discontinuation will be imputed by last observed carried forward. The detailed derivation of the AUC will be provided in the SAP. The AUC will be analyzed using analysis of covariance (ANCOVA) based on FAS-SIGE and FAS-no SIGE separately. The LS means of the treatment difference compared with placebo and 2-sided 95% CI will be presented for each TAK-062 dose group. Nominal p-values will be calculated. No hypothesis testing will be performed.
- Estimands using change in CDSD GI symptom score from Week -3 (before SIGE) and from Week -5 (before study intervention) to Week 12 as the endpoint. The analysis method will be the same as the main estimand. Nominal p-values will be calculated. No hypothesis testing will be performed.

Exploratory analysis: The primary endpoint of change from baseline in CDSD GI symptom severity score at Week 12 will also be analyzed by modeling based on combined FAS-SIGE and FAS-no SIGE excluding the [redacted] SIGE group, where the effects of treatment group, SIGE, and their interaction effects will be estimated in the same model.

13.1.3.2 Secondary Efficacy Endpoint Analysis

The main estimands for the secondary objectives assess the treatment effect of TAK-062 compared with placebo at Week 24 in target population based on the following variable/endpoint:

- Change in Vh:Cd from baseline (measured at Week -4) to Week 24.

The target population, treatments, and ICEs are the same as for the primary estimand in Section 13.1.3.1. Composite strategy will be used to address the ICEs of treatment discontinuation due to lack of efficacy or treatment-related AEs, and treatment policy strategy for the ICEs of SIGE bar discontinuation or rescue medication use (ie, Vh:Cd measured at Week 24 will be used regardless of SIGE bar discontinuation or rescue medication use) and other reasons for discontinuations.

The corresponding population-level summaries are:

- Treatment difference (TAK-062 – placebo) in the change from baseline to Week 24 in average Vh:Cd on duodenal biopsy, for each dose level.

The analysis will be conducted using ANCOVA. The model will include treatment group and the randomization stratification factors as fixed effects and baseline values as covariate. Missing values will be regarded as missing at random. Missing data will be handled using multiple imputation (details will be provided in the SAP). The LS means and 2-sided 95% CI will be provided for the Week 24 treatment difference between the [redacted] TAK-062 dose groups versus placebo, respectively. Nominal 2-sided p-values will be provided for the comparison of [redacted] TAK-062 versus placebo, [redacted] TAK-062 versus placebo, and [redacted] TAK-062 versus placebo, respectively.

Supplementary analyses will be planned as follows:

Supplementary analyses based on subjects who satisfied study entry criteria and are on pre-enrollment diet will be performed. The corresponding endpoints will be analyzed based on FAS–no SIGE.

Supplementary analyses based on the target population excluding subjects who report >1 point improvement in PGIS during [redacted] run-in period will also be performed. The analysis will be performed for FAS-SIGE and FAS-no SIGE separately.

For all the above supplementary analyses, the endpoint definitions, strategy for the ICEs and population-level summary will be the same as for the main estimand. Nominal p-values will be calculated. No hypothesis testing will be performed.

As an exploratory analysis, the endpoint of change from baseline (Week -4) in Vh:Cd measurements at Week 24 will also be analyzed by modeling based on combined FAS-SIGE and FAS–no SIGE excluding the [redacted] TAK-062 [redacted] group, where the effects of treatment group, SIGE and their interaction effects will be estimated in the same model.

The analysis on Vh:Cd will be performed similarly for the changes in the individual Vh and Cd measurements as exploratory analyses.

13.1.3.3 Other Efficacy Endpoint Analyses

The endpoint of change from baseline in CDSD symptom severity item score for each individual symptom and change in each of the frequency questions from the supplemental questions (bowel movements, diarrhea, and vomiting) from Week -1 to Weeks 12 and 24 will be analyzed using the same approach as the primary analysis described in Section 13.1.3.1. The frequency of bowel

movements will be converted to an indicator for constipation (defined as fewer than 3 days of complete spontaneous bowel movement in a week). The weekly average of the frequency items will be an average of each daily frequency during the week, with constipation having values of 0 (no constipation) or 1 (constipation) each week. Weekly frequency will be calculated where the CDSD is completed on at least 4 of the 7 days. When the daily diary is completed on less than 4 of the 7 days, the weekly frequency will be considered missing.

The change in symptom severity for each item in CDSD and in each frequency item in the supplemental questions from Week -3 (before SIGE) and from Week -5 (before study intervention) to Weeks 12 and 24 will also be analyzed. The analysis method will be the same as for the corresponding change from Week -1. Nominal p-values will be calculated. No hypothesis testing will be performed.

PGIC score at Weeks 12 and 24 and the change from baseline in PGIS score will be assessed using analysis of variance model with treatment group and the randomization stratification factors as fixed effects. Other exploratory PRO endpoints at Weeks 12 and 24 will be analyzed using the same approach as in Sections 13.1.3.1 and 13.1.3.2.

Other exploratory histology efficacy endpoints at Week 24, including change from baseline in histology endpoints such as Vh, Cd, IEL, quantitative Marsh, [redacted] for the first tertile of the intestine will be analyzed using the same approach as in Section 13.1.3.2.

For binary endpoints, number and proportion of subjects will be provided for each treatment arm. The comparison between each dose of TAK-062 with placebo will be performed using the Cochran-Mantel-Haenszel test adjusted by the randomization stratification factors. The point estimates for the treatment difference along with 95% CI will be provided. Nominal 2-sided p-values will be provided. Nonresponder imputation will be used for missing data.

All efficacy endpoints will also be summarized by descriptive statistics by treatment group at each visit.

Subgroup analysis will be performed for the efficacy endpoints based on celiac serologic status, symptom severity and symptom type, severity of small intestine mucosal injury, gluten exposure by GIP urine evaluation during the run-in period, and demographics.

13.1.4 PK Analysis

Measured plasma concentrations of TAK-062 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 clinical study report.

13.1.5 [redacted]

[redacted]

13.1.6 Pharmacodynamic Analysis

The analyses for histological endpoints are described in Section 13.1.3.

A detailed description of the pharmacodynamic biomarker analyses related to intestinal gene expression and microbial community changes will be provided in a separate document, and a separate report will be provided.

13.1.7 Psychometric Analyses for CDSD

The psychometric analysis plan (PAP) will also be finalized before the IA. The PAP will provide further details of the analysis methodology for the psychometric evaluation of the CDSD. A separate report will be provided.

13.1.8 Exit Interview Analysis

Exit interviews will be qualitatively analyzed and a separate report will be provided.

13.1.9 Safety Analysis

All safety analyses will be conducted using the SAF, the SAF-SIGE, and the SAF–no SIGE.

No statistical testing or inferential statistics will be generated. All AEs will be coded using the latest MedDRA version. The number and percentage of subjects with TEAEs (new onset or worsening AEs after the first dose of study treatment regardless of relationship to study drug), treatment-related AEs, SAEs, and AEs leading to treatment discontinuation will be summarized by MedDRA primary System Organ Class and Preferred Term, overall and by severity for each treatment group.

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

13.1.10 Immunogenicity Analysis

Each ADA sample will be tested first by a screening test, followed by a confirmatory test if the screening test is positive. An ADA test will be considered positive only when both the screening and confirmatory tests show positive results. Testing for neutralizing antibodies (NAbs) will be performed only if the ADA testing is considered positive. A positive ADA subject is defined as a subject who has at least 1 positive ADA result during the study, and is further categorized as:

- Transiently positive: defined as subjects with confirmed positive ADA in at least 1 sample and no consecutive samples.
- Persistently positive: defined as subjects with confirmed positive ADA in 2 or more consecutive positive ADA samples.

Immunogenicity will be analyzed using the immunogenicity analysis set. Percentage of subjects with positive ADA blood sample results and percentage of subjects with positive neutralizing ADA during the study will be summarized by treatment group. Percentage of subjects with positive ADA will be also summarized by study visit and treatment group. The impact of positive ADA on PK, efficacy, and safety may be evaluated. Results of ADA and NAb tests will be also in listings.

13.2 IA and Criteria for Early Termination

An IA is to be performed to see if clinical efficacy and safety have been demonstrated. The IA will be performed when at least 75% of subjects in Cohort 1 have either completed 12 weeks of treatment or dropped out. The IA will include safety analysis, primary efficacy analysis, and histological data analysis based on available data. The decision to continue Cohort 2 and initiate enrollment of adolescents will be based on the safety evaluation, the conditional power for the primary efficacy analysis, and the analysis of Vh:Cd data. It will not lead to stopping Cohort 1 for efficacy or futility. Thus, there will be no alpha level adjustment for the final analysis.

Safety Considerations

Safety will focus on the severity of reported adverse events. When the proportion of subjects with Grade ≥3 events related to TAK-062 is more than 20% (percentage points) higher in the active arm than in the placebo arm, safety will be considered not acceptable and may lead to early termination of the study.

Efficacy Considerations

For efficacy, the recommendation chart with conditional powers for CDSD GI symptom severity score and the probability of Vh:Cd will be used for decision making by the IDMC in conjunction with their clinical evaluation of the totality of the study data per Table 13.a.

The conditional power will be calculated on the basis of the test statistic in the MMRM model of the primary efficacy endpoint at Week 12, and the probability for Vh:Cd at Week 24 will be documented in the SAP.

The recommended decision criteria based on the conditional power for CDSD GI symptom severity score and the probability of Vh:Cd, after significant safety concerns are ruled out, are shown in Table 13.a.

Table 13.a [redacted]

[redacted]

Table 13.a [redacted]

The study will be completed as planned unless 1 or more of the criteria are satisfied that require temporary suspension or early termination of the study as described in Section 6.3.

13.3 Determination of Sample Size

The planned sample size is approximately 357 subjects. For a 2-sample comparison of means, 0.5 standardized mean difference is regarded as a medium effect size (Levin 1997). A sample size of 53 subjects per treatment group will provide 80% power to detect a standardized mean difference (mean difference/SD) of 0.55 between [redacted] TAK-062 and placebo in the change from baseline CDSD weekly score (assuming common SD) for a 2-sided statistical hypothesis test, using a 2-sample t-test and a 5% significance level. Assuming a dropout rate of approximately 12%, a sample size of 60 subjects per treatment group for the [redacted] and placebo arms in the gluten-containing SIGE group in Cohort 1 will be the planned enrollment.

The planned enrollment for Cohort 2 is 30 and 50 adults per treatment arm in the placebo and active arms ([redacted] TAK-062), respectively, in the gluten-containing SIGE arms; 50 subjects (43 adults and 7 adolescents) per arm in the [redacted] and placebo gluten-free SIGE bar arms; and 7 (adolescents only) in the [redacted] gluten-free SIGE bar arm.

For the combined placebo gluten-containing SIGE groups from Cohorts 1 and 2 versus [redacted] TAK-062, 86% power would be provided (based on the 2-sample t-test and the 5% significance level) to detect the standardized mean difference between groups (0.55) with the same 12% assumption for dropout rate. In addition, 82% power would be provided from the same assumptions for combined placebo gluten-containing SIGE group from Cohorts 1 and 2 versus [redacted] TAK-062 group. The analysis to detect the difference between the combined placebo gluten-containing SIGE group and the active group would yield a higher power.

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 guarantees access to source documents by the sponsor and/or its designee (contract research organization) and by the IRB or IEC. 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/pediatric assent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent/pediatric assent forms), 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 or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria. Before implementing changes in the study, the sponsor and the IRB/IEC must approve any revisions of all informed consent/pediatric assent documents and amendments to the protocol unless there is a subject safety issue.

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 or IEC, 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.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees 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 ICH GCP Guideline E6 (1996), European Union Directive

2001/20 EC, as well as all local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent/pediatric assent and investigator responsibilities.

15.1 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique ID 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 and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's 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/pediatric assent process (see Section 15.3).

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

15.2 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this 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.

Before implementing changes in the study, the sponsor and the IRB/IEC must approve any revisions of all informed consent/pediatric assent documents and amendments to the protocol unless there is a subject safety issue.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the informed consent/pediatric assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be

submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent/pediatric assent must be obtained and submitted to the sponsor or designee before commencement of the study supplied drug or study-specific screening activity/signing a contract for the clinical study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent/pediatric assent form) reviewed; and state the approval date. The sponsor will notify site 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, no protocol activities, including screening, may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent/pediatric assent form, 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 or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

15.3 Subject Information, Informed Consent/Pediatric Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent/pediatric assent 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 informed consent/pediatric assent form, 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 informed consent/pediatric assent forms 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/pediatric assent is given. The informed consent/pediatric assent forms will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The informed consent form, pediatric assent form, 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 informed consent form, pediatric assent form, subject authorization form (if applicable),

and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent/pediatric assent, 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 informed consent/pediatric assent forms 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 informed consent/pediatric assent forms and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent/pediatric assent forms, 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/pediatric assent forms in the subject's medical record. Copies of the signed informed consent/pediatric assent forms, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent/pediatric assent forms 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 informed consent/pediatric assent forms.

Physical and emotional pain for children will be addressed and minimized as much as possible during the trial. For procedures, analgesia will be provided per a professional at a site with experience in caring for and treating physical and emotional pain in patients at this age, and pain monitored and treated per standard of care. Blood draws may utilize lidocaine, numbing agents and smaller caliber needles (butterfly needles). It should be noted that pediatric patients are not included in the additional PK intensive blood draws.

The volume of blood drawn will not surpass weekly or monthly safety limits for subjects ≥33 kg. If a subject's weight is <33 kg, a screening blood draw may be done on 2 consecutive weeks, as to not surpass the weekly blood draw limit.

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, is the sole responsibility of the sponsor.

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Biagi, F., Campanella, J., Martucci, S., Pezzimenti, D., Ciclitira, P. J., Ellis, H. J., et al. 2004. A milligram of gluten a day keeps the mucosal recovery away: a case report. *Nutr Rev,* 62(9), 360-3.

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Appendix A Schedule of Study Procedures

Assessment	Screening	Run-in	Treatment Period				Safety Follow-up
	Visit 1	Visit 2	Visit 3 [a]	Visit 4 [a]	Visit 5	Visit 6/ET	Visit 7 [a]
	Week -8	Week -4	Week 0	Week 3	Week 12	Week 24	Week 28
	Day -56 to Day -42	Day -30 to -20	Day -2 to Day 1 (at least 21 days after Visit 2)	Day 21 ± 5 days	Day 84 ± 5days	Day 168 ± 5 days	Day 196 ± 5 days
General Study Conduct							
Informed consent/pediatric assent	X						
Inclusion/exclusion criteria	X [b]	X	X				
Demographics	X						
Medical history	X						
Medication history	X						
GFD quiz	X						
Physical examination (including height and weight)	X	X				X	
Vital signs	X	X				X	
ECG		X				X	
Concomitant medications	X	X	X	X	X	X	X
PTE/AE assessment	X	X	X	X	X	X	X
Placebo response reduction/accurate symptoms reporting [c]	X	X	X				
Exit interview [d]						X	
Clinical laboratory tests (serum, urine, and other)							
Clinical laboratory evaluations (hematology and chemistry)	X	X	X [a]	X [a]	X	X	X [a]
Urinalysis [e]	X			X	X	X	X
Pregnancy test (hCG) [f]	X	X	X	X	X	X	X
FSH [g]	X	X					
HLA testing	X						

	Screening	Run-in	Treatment Period				Safety Follow-up
	Visit 1	Visit 2	Visit 3 [a]	Visit 4 [a]	Visit 5	Visit 6/ET	Visit 7 [a]
	Week -8	Week -4	Week 0	Week 3	Week 12	Week 24	Week 28
Assessment	**Day -56 to Day -42**	**Day -30 to -20**	**Day -2 to Day 1 (at least 21 days after Visit 2)**	**Day 21 ± 5 days**	**Day 84 ± 5days**	**Day 168 ± 5 days**	**Day 196 ± 5 days**
Clinical laboratory tests (serum, urine, and other [cont.])							
Celiac serologies	X				X	X	
Drug assignment, administration, and accountability							
Study drug administration [h]		X----------X					
[redacted]							
Randomization to treatment			X [i]				
Study drug accountability		X	X	X	X	X	
[redacted]							
PK/biomarkers							
Qualitative GIP [j]	X	X----------X					
Quantitative GIP [k]	X	X	X	X	X	X	X
Plasma sample for PK and biomarkers [l]		X	X	X	X	X	X
Serum sample for ADA and biomarkers [m]		X	X	X	X	X	X
EGD		X				X	
Sigmoidoscopy with biopsy [n]		X					
[redacted]							

Assessment	Screening	Run-in	Treatment Period				Safety Follow-up
	Visit 1	Visit 2	Visit 3 [a]	Visit 4 [a]	Visit 5	Visit 6/ET	Visit 7 [a]
	Week -8	Week -4	Week 0	Week 3	Week 12	Week 24	Week 28
	Day -56 to Day -42	Day -30 to -20	Day -2 to Day 1 (at least 21 days after Visit 2)	Day 21 ± 5 days	Day 84 ± 5days	Day 168 ± 5 days	Day 196 ± 5 days
PROs [p]							
CDSD v2.1 [q]	X----------						----------X
EQ-5D-5L CeD Most Bothersome Symptom PROMIS—Fatigue Instrument [r] PROMIS–Cognitive Function Instrument [s] CeD-GSRS [t] WPAI:SHP–CeD SF-12 v2 ICDSQ CDAQ CD-QoL	X		X		X	X	
PGIS [u]	X	X	X	X	X	X	
PGIC			X		X	X	

ADA: antidrug antibody; AE: adverse event; CDAQ: Coeliac Disease Questionnaire; CD-QoL: Celiac Disease Quality of Life; CDSD: Celiac Disease Symptom Diary; CeD: celiac disease; CeD-GSRS: Celiac Disease Gastrointestinal Symptom Rating Scale; [redacted] cont.: continued; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; EGD: esophagogastroduodenoscopy; EOT: end of treatment; EQ-5D-5L: EuroQol-5 Dimension-5 Levels; ET: early termination; FSH: follicle-stimulating hormone; GFD: gluten-free diet; GIP: gluten immunogenic peptide; hCG: human chorionic gonadotropin; HLA: human leukocyte antigen; ICDSQ: Impact of Celiac Disease Symptoms Questionnaire; IRT: interactive response technology; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: pharmacokinetic(s); PRO: patient-reported outcome; PROMIS: Patient-Reported Outcomes Measurement Information System; PTE: pretreatment event; SIGE: simulated inadvertent gluten exposure; SF-12: Short Form 12-Item; [redacted]; US: United States; v: Version; [redacted]; WPAI+CIQ:CeD: Work Productivity and Activity Impairment Plus Classroom Impairment Questionnaire: Celiac Disease.

[a] Visits 3, 4, and 7 may be conducted virtually or at home at the discretion of the investigator due to reasons including but not limited to COVID-19. Clinical laboratory evaluations may be omitted per investigator discretion based on ongoing safety monitoring of the subject.

[b] Subjects will ingest a gluten-free SIGE bar to confirm tolerability of nongluten ingredients as per exclusion criteria.

[c] Once training is available, subjects may receive training at Visits 1, 2, and 3, as well as at Weeks 6, 10, 16, and 22.

[d] Conducted only in a subset of subjects at selected sites in the US and will be scheduled within 10 days of the EOT visit or early termination.

[e] Urinalysis for safety assessment.

[f] Serum pregnancy test at Week -8; all others are urine pregnancy tests.

[g] FSH test will be done at least twice (at Visit 1 and 2) for those subjects who are amenorrheic for less than 12 months (see Section 9.3.13.3).

[h] At the first visit (Week -8), subjects will consume 1 gluten-free SIGE bar and will be excluded if they develop significant symptoms suggestive of a confounding food intolerance. During the single-blind run-in period (Week -4 through Day -1), subjects will receive TAK-062 placebo [redacted]. From Week 0 through the 24-week treatment period, subjects will receive gluten-containing SIGE food bar in Cohort 1 and blinded gluten-containing SIGE or gluten-free SIGE [redacted] in Cohort 2, with a meal after taking TAK-062 or placebo taken [redacted] before the start of a meal.

[i] In the event that Visit 3 is unable to be conducted at the study site, this will be a telehealth visit to witness the subject taking study medication. The first dose of study drug administered may come after the randomization transaction due to time for shipment of study drug to the subject's home after randomization in IRT. In this instance, the schedule of events will be calculated from the date of first dose of study drug administration (Day 1).

[j] First morning void to be collected in standard urine collection cups for GIP testing weekly throughout the study. [redacted] While all efforts should be made to obtain weekly urine samples, missed urine GIP samples will not be considered a protocol deviation.

[k] On the day of a clinic visit, subjects will collect the first morning void in [redacted] and take the sample to the site. [redacted]

[l] Refer to Appendix B for information about the PK collection schedule. Predose collections for exploratory analysis of biomarkers will be performed at the same visit as PK sampling. Predose plasma and serum samples are also being collected to enable evaluation [redacted] and how they respond to treatment. These collections may be useful for noninvasive patient selection or disease monitoring.

[m] A predose ADA will be taken on the same days as PK sample collection according to Appendix B. Predose collections for exploratory analysis of biomarkers will be performed at the same visit as PK sampling. Predose plasma and serum samples are also being collected to enable [redacted] and how they respond to treatment. These collections may be useful for noninvasive patient selection or disease monitoring.

[n] At the time of the endoscopy, sigmoidoscopy with biopsy may be performed in subjects with diarrhea as their predominant symptom at the discretion of the investigator if there is a concern for active microscopic colitis as a cause of symptoms.

[redacted]

[p] All PROs should be done, if possible, before any other procedures and in the following order: EQ-5D-5L, PGIS, PGIC, CeD Most Bothersome Symptom, PROMIS—Fatigue Instrument appropriate to the age of the subject; GSRS, PROMIS—Cognitive Function Instrument appropriate to the age of the subject, WPAI+CIQ:CeD, SF-12 v2, ICDSQ, CDAQ, and CD-QoL.

[q] CDSD v2.1 and supplemental frequency questionnaire should be completed daily around the same time every day.

[r] PROMIS—Fatigue Instrument: For subjects aged 12-17 years, administer the PROMIS Pediatric Item Bank v2.0—Fatigue—Short Form 10a: Pediatric Fatigue; for subjects ≥18 years, administer the PROMIS Item Bank v1.0—Fatigue—Short Form 13a.

[s] PROMIS—Cognitive Function Instrument: For subjects aged 12-17 years, administer the PROMIS Pediatric Item Bank v1.0—Cognitive Function—Short Form 7a: Pediatric Cognitive Function; for subjects ≥18 years, administer the PROMIS Item Bank v2.0—Cognitive Function—Short Form 6a.

[t] CeD-GSRS will also be performed at Week -7 (for validation purposes).

[u] PGIS will also be performed at Weeks -8 and -7 (for validation purposes) and Week -2. On Day 0, PGIS should be performed prior to randomization. The volume of blood drawn will not surpass weekly or monthly safety limits for subjects ≥33 kg. If a subject's weight is <33 kg, a screening blood draw may be done on 2 consecutive weeks, as to not surpass the weekly blood draw limit.

Appendix B Schedule of PK Samples

Study Time (Week/Day)	Week -4/ Visit 2	Week 0/Randomization/Visit 3		Week 3/Visit 4		Week 12/ Visit 5	Week 24/ Visit 6/ET	Week 28/ Safety Follow-up
Sampling time (h)	All Subjects	PK Subgroup	All Other Subjects [a]	PK Subgroup [b]	All Other Subjects [b]	All Subjects	All Subjects	All Subjects
Predose	X [d]	X	X	X	X	X	X [d]	X [d]
0.5		X	X	X	X	X		
1		X	X	X	X	X		
2		X	X [c]	X	X [c]	X [c]		
3		X	X [c]	X	X [c]	X [c]		
4		X [c]		X [c]		X [c]		

ET: early termination; h: hour; hr: hour; PK: pharmacokinetics.

PK sampling times are relative to the most recent dose (in hours). The actual date and time of the sample collection and the date and time for the current dose and the dose before the in-clinic dose should be accurately recorded. PK sampling time windows are as follows: predose sample (up to 30 minutes prior to dosing), postdose samples at 0.5 hr (±5 minutes), 1 hr (±10 minutes), 2 hr (±10 minutes), 3 hr (±15 minutes), and 4 hr (±15 minutes). A predose antidrug antibody sample should be collected any time PK collections occur for all subjects.

[a] If a subject not in the PK subgroup is unable to complete the visit in clinic, PK sampling at this visit will be optional.

[b] If subjects are unable to complete the visit in clinic, subjects may choose to delay their PK collection to a later date but before their Week 12 visit as an unscheduled visit following the same collection schedule noted in Visit 4 or complete collections via home healthcare during Visit 4.

[c] Optional sample collection.

[d] One blood sample collected at any time during the visit.

Appendix C Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 56, 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/IEC. Each informed consent/pediatric assent forms 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 informed consent/pediatric assent forms does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

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

Appendix D 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/IEC, and the monitor may inspect the records. By signing a written informed consent/pediatric assent forms, the subject 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/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject 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 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 informed consent/pediatric assent forms 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) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    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.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 40 days after the last dose. 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 effective contraception (as defined in the informed consent) from signing the informed consent/pediatric assent forms throughout the duration of the study, and for 100 days after the last dose. If the partner or wife 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 trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix E Investigator Consent to Use of Personal Information

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

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

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

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

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

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

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

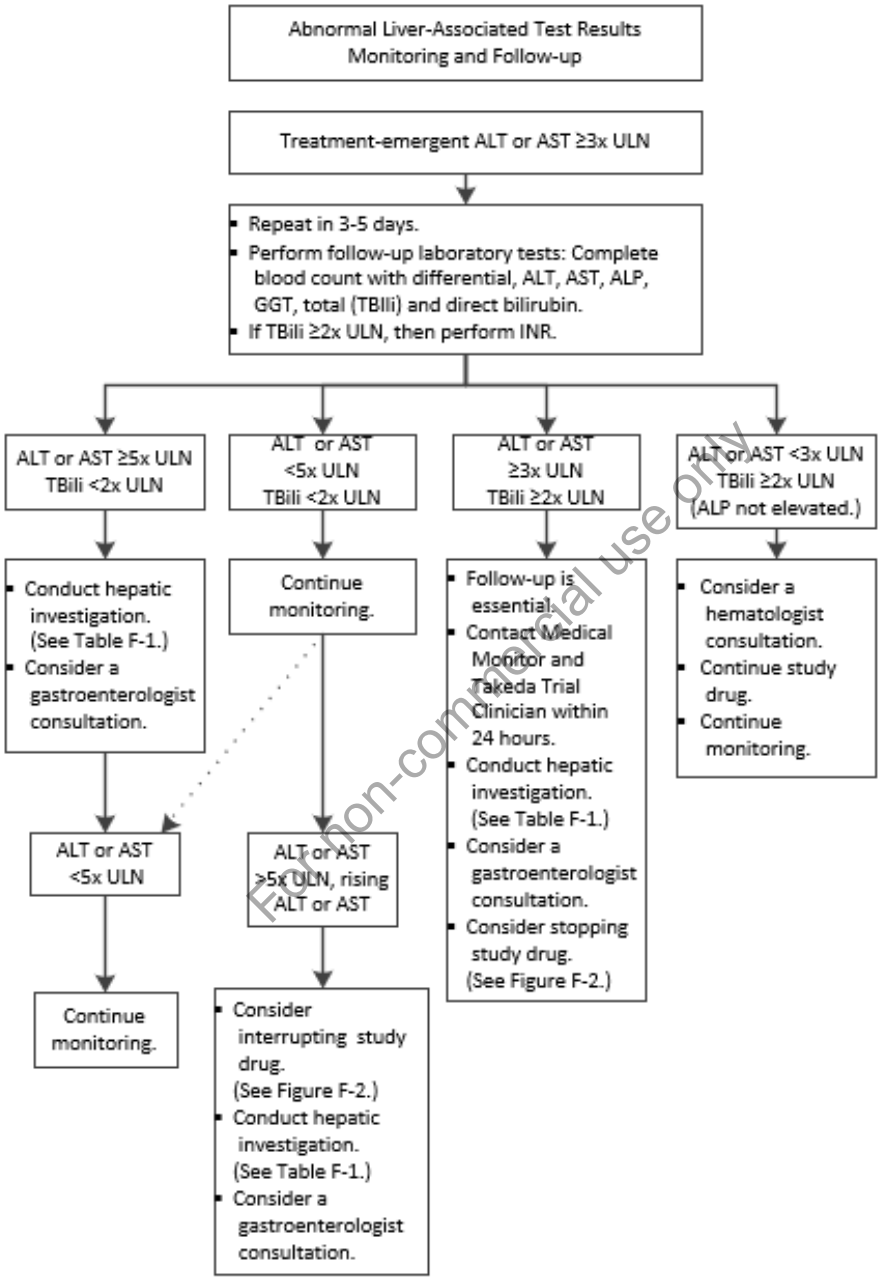
Investigators must be vigilant for abnormal liver test results in subjects during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical study subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This 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 <3 × the ULN, total bilirubin <1.5 × ULN, and alkaline phosphatase <1.5 × ULN) at the time of enrollment.

In evaluating study 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 F-1. Suggested hepatic investigations are listed in Table F-1.

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 within 24 hours. Hepatic investigations as suggested in Table F-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.

Figure F-1 Liver Test Abnormality Monitoring and Follow-up

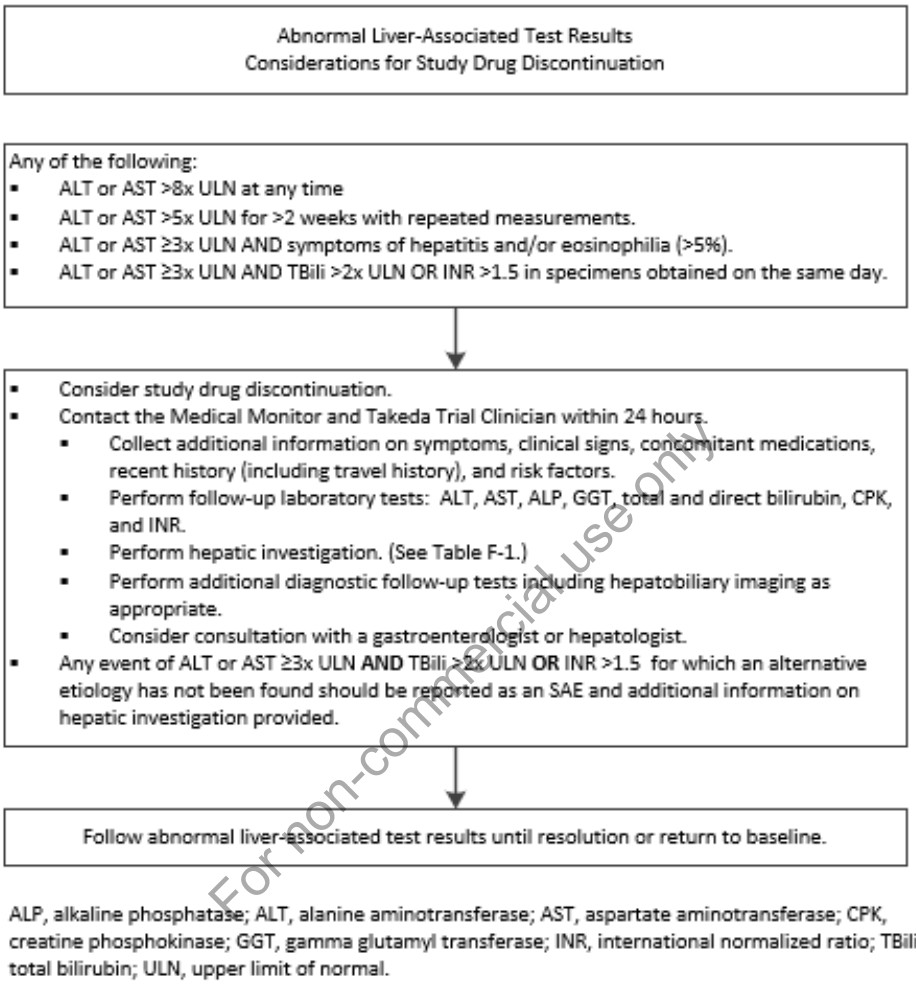


ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; TBili, total bilirubin; ULN, upper limit of normal.

Table F-1 Hepatic Investigation

Medical history	• Concomitant medications (including over-the-counter 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, hepatitis B surface antibody, hepatitis B core antibody (IgM anti-HBc), hepatitis C antibodies. • Hepatitis E (IgG and IgM). • Consider polymerase chain reaction for hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen, Epstein-Barr nuclear antigen, early antigen). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	• Antinuclear antibody. • Antismooth muscle antibody. • Anti–liver-kidney microsomal antibody.

Figure F-2 Liver Test Abnormalities: Considerations for Study Drug Discontinuation



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

Table F-2 Drug-Induced Severity Grading Scales

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 and INR ≥1.5
3 Moderate to Severe	Elevated ALT, ALP, TBL, and/or INR and 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 criteria:
	Hepatic failure (INR >1.5, ascites, or encephalopathy)
	Other organ failure due to DILI
5 Fatal	Death or liver transplantation to due DILI

Source: United States Drug Induced Liver Injury Network.

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

Appendix G Rescue Medications

If these medications are not available, alternatives may be used after discussion with the medical monitor.

Anti-diarrheal medications

Lomotil (diphenoxylate hydrocholoride 2.5 mg/atropine 0.025 mg): 2 tablets orally every 6 hours as needed for diarrhea (maximum 20 mg/day of diphenoxylate hydrochloride). Loperamide is acceptable if Lomotil not available in the study country and administered as 2 mg orally every 4 hours as needed for diarrhea (maximum 1 6 mg daily).

Antinausea/antiemetic medications

Ondansetron 4 mg orally every 12 hours as needed for nausea/vomiting.

Antispasmodic medications

- Dicyclomine or hyoscyamine: 10 mg orally every 6 hours as needed for abdominal spasm.
- Hyoscine butylbromide (Buscopan): 10 mg orally every 6 hours as needed for abdominal cramping.
- Mebeverine (Duspatalin): 135 mg orally TID as needed for abdominal spasm.
- Phloroglucinol (Flospan): 160 mg orally (2 80 mg tablets) for abdominal spasms; repeat every 2 or more hours as needed to a maximum of 6 tablets (480 mg) in 24 hours.
- Otilonium bromide (Spasmomen): 40 mg orally TID as needed for abdominal spasm.
- Trimebutine (Trimedine): 200 mg orally TID before meals as needed for spasms.
- Peppermint oil.

Appendix H Protocol History

Date	Amendment Number	Amendment Type	Region
16 November 2023	5	Substantial	Global
02 June 2023	4	Substantial (not submitted to sites)	Global
26 October 2022	3	Substantial	Global
22 July 2022	2	Substantial	Global
23 June 2022	1	Substantial	Global
18 January 2022	Initial protocol	Not applicable	Global

Protocol Amendment 4 Summary and Rationale:

This document describes the changes to the protocol incorporating Amendment 4. The primary reason for this amendment is to update inclusion and exclusion criteria, contraception requirements, and rescue medication instructions.

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 4			
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	Updated the number of sites.	To increase recruitment rate.
2.	Section 2.0 STUDY SUMMARY	Corrected error in the study design diagram.	Correction.
3.	Section 2.0 STUDY SUMMARY	The broad term 'mucosal injury' was replaced with a specific description 'villous atrophy'.	Clarification.
4.	Section 2.0 STUDY SUMMARY Section 4.1 Background Section 4.3 Benefit-Risk Profile Section 6.1 Study Design Section 13.2 IA and Criteria for Early Termination	Clarified the inclusion of adolescents in Cohort 2 by stating "If efficacy and safety data from Cohort 1 is considered acceptable, Cohort 2 will also include adolescents aged 12 to 17 years, inclusive".	Enrollment of adolescent subjects into Cohort 2 is contingent upon independent data monitoring committee (IDMC) review.
5.	Section 2.0 STUDY SUMMARY Section 5.2.3 Safety Endpoints	Clarified the safety endpoint of immunogenicity is posttreatment positive antidrug antibodies.	Clarification.

Protocol Amendment 4			
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***
6.	Section 2.0 STUDY SUMMARY Section 5.2.4 Exploratory/Additional Endpoints Section 6.2.3.1 Efficacy Section 6.2.3.4 Urine-Based Biomarker: GIP	Revised "weekly" to "once per week".	Clarification.
7.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	[redacted]	Corrected error.
8.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Clarified that TAK-062 will be consumed immediately prior to meals instead of with meals.	Clarification.
9.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 9.3.5 GFD Knowledge Quiz	Clarification that it is at the investigator's discretion if the subject has adequate comprehension of a gluten-free diet (GFD).	Clarification.
10.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	In the study summary and Inclusion Criterion 9, removed the upper age limit, and added "Inclusion of subjects older than 75 years of age may be discussed with the study medical monitor."	To allow subjects older than 75 years to be enrolled.
11.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	[redacted]	[redacted].
12.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	In the study summary and Exclusion Criteria 7, clarified "evaluable" days and changed from Week -8 to the run-in period.	Clarification
13.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	In the study summary and Exclusion Criterion 9, "small intestinal bacterial overgrowth" was added.	To clarify that subjects with small bacterial overgrowth will be excluded.

Protocol Amendment 4			
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***
14.	Section 2.0 STUDY SUMMARY Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	The description of the study population was simplified.	Clarification.
15.	Section 3.2 Coordinating Investigator	Clarified that a signatory coordinating investigator "may" be selected instead of "will" be selected.	Clarification.
16.	Section 4.1 Background	Added intraepithelial lymphocyte infiltration. Clarified "utility of quantitative and qualitative endpoints".	Clarifying the main histologic observations and scoring criteria used in assessing celiac disease (CeD) tissues for histology. Both quantitative and qualitative scoring methods measure mucosal injury and cellularity to grade severity.
17.	Section 4.3 Benefit-Risk Profile Section 6.2.2 Rationale for Dose	Updated text to reflect 1 unrelated SAE has been reported in the clinical program.	Updated information.
18.	Section 6.1 Study Design Section 6.2.3.4 Urine-Based Biomarker: GIP Appendix A Schedule of Study Procedures	Clarified consumption of SIGE bar related to gluten immunogenic peptide (GIP) urine collection.	Clarification.
19.	Section 6.1 Study Design Section 9.3.10 [redacted] Section 13.3 Determination of Sample Size	[redacted]	[redacted]
20.	Section 6.1 Study Design	Clarified all subjects will have sparse pharmacokinetic (PK) blood samples taken.	Clarification.
21.	Section 6.1 Study Design Section 9.3.12.1 Collection of Blood and Plasma for PK Sampling	Clarified randomization is Week 0.	Clarification.

Protocol Amendment 4			
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***
22.	Figure 6.a Schematic of Study Design	Corrected error in figure.	Correction.
23.	Section 7.1 Inclusion Criteria	In Inclusion Criterion 3, removed "after viewing of educational materials".	Correction.
24.	Section 7.1 Inclusion Criteria	In Inclusion Criterion 10, added "Subjects 12 to 18 years of age will only be included after IDMC review".	Clarification.
25.	Section 7.1 Inclusion Criteria	In Inclusion Criterion 12, added a note that individuals with body mass index (BMI) of 40 to 45 should be discussed with the medical monitor and confirmed to be appropriate for endoscopy according to local site guidelines.	To allow the subjects with a BMI up to 45 to be enrolled in the study
26.	Section 7.1 Inclusion Criteria	[redacted]	[redacted]
27.	Section 7.2 Exclusion Criteria Section 7.3 Excluded Medications	[redacted]	[redacted]
28.	Section 7.2 Exclusion Criteria	In Exclusion Criterion 23, revised language regarding coronavirus disease 2019.	Clarification
29.	Section 7.2 Exclusion Criteria Section 7.3 Excluded Medications	Clarified the use of stable doses (ie, more than 4 weeks) of an osmotic, bulking-forming or emollient (surface active agent) laxative is allowed.	Clarification

Protocol Amendment 4			
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***
30.	Section 7.4 Rescue Medications	Clarified instructions for use of all medications (prescriptions and over-the-counter medications), if needed, will be obtained from the study physician. Removed 'time' from the information provided for each occurrence of rescue medication. Added "during the treatment period (after randomization)".	Clarification
31.	Section 9.3.1 Physical Examination Procedure	Revised the timing of a baseline physical examination from before the first dose of study drug to during Visit 1.	Clarification
32.	Section 9.3.3 Vital Sign Procedure	Specified positions for vital sign readings.	Clarification
33.	Section 9.3.7.1 Accurate Symptom Reporting Training Section 9.3.7.2 Placebo Response Reduction Training Appendix A Schedule of Study Procedures	Clarified that subjects may receive training once training is available.	Clarification.
34.	Section 9.3.7.4 Research Subject Responsibilities Training	Added section on Research Subject Responsibilities training.	Inadvertently admitted previously.
35.	Section 9.3.8 Exit Interview – United States Only Appendix A Schedule of Study Procedures	Specified the exit interview will take place in the United States only.	Clarification.
36.	Section 9.3.8 Exit Interview – United States Only	Clarified only consented subjects would be invited to participate in exit interviews.	Clarifications.
37.	Section 9.3.8 Exit Interview – United States Only	Clarified important or meaningfulness of perceived benefits of treatment included symptom-free and minimal symptom days.	Clarifications.

Protocol Amendment 4			
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***
38.	Section 9.3.12.1 Collection of Blood and Plasma for PK Sampling Appendix B Schedule of PK Samples	Requirement for providing PK samples at specific time points changed from Week 24 to Week 12. At Week 24, PK samples are now collected at any time during the visit. PK sampling times changed from percentage-based nominal times, to fixed time points in relation to dose.	Rich PK sampling changed from Week 24 to Week 12 to provide flexibility and to minimize the number of scheduled procedures at Week 24, which includes an esophagogastroduodenoscopy (EGD) evaluation.
39.	Section 9.3.13.1 Male Subjects and Their Female Partners Section 9.3.13.3 Definitions and Procedures for Contraception and Pregnancy Avoidance Table 9.b Acceptable Contraception Methods and Lactation Guidance for This Study Appendix D Elements of the Subject Informed Consent	[redacted]	[redacted]
40.	Section 9.3.16 Documentation of Screen Failure	Added rescreening will not be allowed for a negative human leukocyte antigen (HLA) test.	Clarification
41.	Section 9.3.9 Endoscopy and Biopsy Collection	Added qualitative morphometric analysis to quantitative analysis.	Clarification

Protocol Amendment 4			
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***
42.	Section 9.3.9 Endoscopy and Biopsy Collection	Removed details of biopsy preparation.	Information provided in the section twice. Duplicate information removed.
43.	Section 9.3.16 Documentation of Screen Failure	Clarified rescreening for subjects who failed due to VH:CD >2.5 or negative HLA testing.	Clarification
44.	Section 9.6 Biological Sample Retention and Destruction	Removed "Notify sponsor of consent withdrawal".	Correction.
45.	Section 10.1.3 Additional Points to Consider for PTEs and AEs	Added overdose definition.	Clarification
46.	Section 11.1 IDMC	Clarified the drug will be safe and efficacious before dosing adolescents.	Clarification
47.	Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	Removed redundant text to simplify subject population attribute description for the primary estimand.	Edited for brevity.
48.	Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	Removed "Estimand with the target population excluding subjects who report >1 point improvement in Patient Global Impression of Severity (PGIS) during [redacted] run-in period. The supplementary analysis will be performed for full analysis set (FAS)-SIGE and FAS–no SIGE separately. The endpoint definition, strategy for the intercurrent events (ICEs) and population-level summary will be the same as the main estimand. Nominal p-values will be calculated. No hypothesis testing will be performed" from supplementary analyses for primary estimand.	Error, repeated twice.
49.	Section 13.1.3.3 Other Efficacy Endpoint Analyses	Removed "Marsh-Oberhuber".	Correction as quantitative Marsh was already present.

Protocol Amendment 4			
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***
50.	Section 13.3 Determination of Sample Size	[redacted]	[redacted]
51.	Appendix A Schedule of Study Procedures	Revised timeline window at Visit 2 and 3.	Clarification
52.	Appendix A Schedule of Study Procedures	Add "On Day 0, PGIS should be performed prior to randomization."	Clarification.
53.	Appendix B Schedule of PK Samples	Added Week 24/Visit 6/ET PK samples.	Rich PK sampling changed from Week 24 to Week 12 to provide flexibility and to minimize the number of scheduled procedures at Week 24, which includes an EGD evaluation.
54.	Appendix F Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up	[redacted]	[redacted]
55.	Appendix G Rescue Medications	[redacted]	[redacted]

Protocol Amendment 3 Summary and Rationale:

This document describes the changes to the protocol incorporating Amendment 3. [redacted]

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 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.	Section 2.0 STUDY SUMMARY	Added statement that urine samples will be collected to check the levels of peptides associated with gluten ingestion during the screening.	Unintentional omission.
2.	Section 2.0 STUDY SUMMARY	Revised the number of study sites.	Increased to support study recruitment.
3.	Section 2.0 STUDY SUMMARY Section 4.1 Background Section 6.2.1 Rationale for Study Design	Added wording to clarify adolescents receive only gluten-free simulated inadvertent gluten exposure (SIGE) bars.	Clarification of gluten exposure to adolescents.
4.	Section 2.0 STUDY SUMMARY Section 4.1 Background Section 4.3 Benefit-Risk Profile Section 6.1Study Design Section 11.2 IRC (deleted)	[redacted]	[redacted]
5.	Section 2.0 STUDY SUMMARY Section 5.2.4 Exploratory/Additional Endpoints Section 6.1 Study Design Section 7.1 Inclusion Criteria Section 9.3.17 (formerly Section 9.3.16) Documentation of Randomization	Villous height to crypt depth ratio (Vh:Cd) revised.	To more accurately capture active celiac disease.
6.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Table 8.b Dose and Regimen	[redacted]	[redacted]
7.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 6.2.1Rationale for Study Design Table 8.b Dose and Regimen Section 13.3 Determination of Sample Size	[redacted]	[redacted]

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***
8.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12	Revised exclusion criterion to add a maximum of 20% of adult subjects without a producible initial biopsy report to be included if they have serology or histology confirmation at screening.	To improve inclusivity, acknowledging many celiac patients may not have their initial pathology report.
9.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added aspartate aminotransferase (AST) ≥3 × upper limit of normal (ULN) as an exclusion criterion.	This was added for consistency, given AST elevation is defined in treatment discontinuation.
10.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added clarification that systemic corticosteroids may be given for endoscopies.	Clarification of corticosteroid usage.
11.	Section 2.0 STUDY SUMMARY Section 7.4 Rescue Medications Section 9.3.15 Documentation of Concomitant Medications Section 13.1.3.2 Secondary Efficacy Endpoint Analysis Section 7.4 Rescue Medications	[redacted]	[redacted]
12.	Section 2.0 STUDY SUMMARY Section 13.1.3.1 Primary Efficacy Endpoint Analysis: Change From Baseline in Weekly CDSD GI Symptom Severity Score at Week 12 Section 13.3 Determination of Sample Size	[redacted]	[redacted]
13.	Section 4.3 Benefit-Risk Profile	A statement regarding the potential risk and subsequent monitoring of antidrug antibodies was added.	To align with the TAK-062 investigator's brochure.
14.	Section 5.2.4 Exploratory/Additional Endpoints Appendix A Schedule of Study Procedures	Revised change from baseline from Week -4 to Week -8 for celiac serology titers.	Corrected error.

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***
15.	Section 6.2.3.1 Efficacy	[redacted]	[redacted]
16.	Section 6.2.3.4 Urine-Based Biomarker: GIP Appendix A Schedule of Study Procedures	Collection of urine in a separate container was added for quantitative analysis of gluten peptides.	Added for clarity.
17.	Section 7.2 Exclusion Criteria	[redacted]	[redacted]
18.	Section 7.6 Criteria for Discontinuation or Withdrawal of a Subject Section 7.7 (formerly Section 7.6) Procedures for Discontinuation or Withdrawal of a Subject	[redacted]	[redacted].
19.	Section 7.7 (formerly Section 7.6) Procedures for Discontinuation or Withdrawal of a Subject	[redacted]	[redacted]
20.	Section 7.7 (formerly Section 7.6) Procedures for Discontinuation or Withdrawal of a Subject	[redacted]	[redacted]
21.	Section 8.1.4 Overdose	Added the statement "There is no experience with overdose with any of TAK-062 formulations."	To align with the TAK-062 investigator's brochure.

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***
22.	Section 8.4 Study Drug and SIGE Blind Maintenance	Added clarification that in the event that results must be reported to the investigator before breaking the blind, all efforts should be made to maintain the blind. Removed instructions that subjects, site staff, and study team members were to remain blinded to the CDSD [redacted]	Subjects, site staff, and study team members will remain blinded to treatment assignments; however, the CDSD [redacted] will not be masked.
23.	Section 9.3.13.1 Male Subjects and Their Female Partners	Added clarification that female partners must also use a highly effective method of contraception. Also clarified sexual abstinence is not an acceptable method of contraception for individuals sexually active with a partner of the opposite sex in which childbearing is a potential outcome.	Clarification of contraception and abstinence.
24.	Section 9.3.7 Placebo Reduction Plan Appendix A Schedule of Study Procedures	Added section describing the placebo reduction plan which includes accurate symptom reporting training, placebo response reduction training, and participant scorecard.	To further elaborate on plan for placebo reduction.
25.	Section 10.1.3 Additional Points to Consider for PTEs and AEs	Clarification that adverse events (AEs) related to gluten should not be reported as an AE unless requiring an intervention such as rescue medication.	To better define AE in context of gluten related symptoms
26.	Section 13.1.7 Psychometric Analyses for CDSD	[redacted]	[redacted].

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*
27.	Section 15.3 Subject Information, Informed Consent/Pediatric Assent, and Subject Authorization	Added information regarding physical and emotional pain of children.	To ensure clarity that the comfort of pediatric subjects is being addressed.

Protocol Amendment 2 Summary and Rationale:

This document described the changes to the protocol incorporating Amendment 2. The primary reasons for this amendment were to:

- Add an exclusion criterion for subjects with known history of hypersensitivity, idiosyncratic reaction, or intolerance to any ingredients or excipients in TAK-062 and/or placebo.
- Add details for tablet administration of TAK-062 and placebo.

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 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 7.2 Exclusion Criteria	[redacted]	[redacted]
2.	Table 8.a Dose and Regimen Table 8.b Dose and Regimen	[redacted]	[redacted]

Protocol Amendment 1 Summary and Rationale:

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

- Add exclusion criteria for subjects with a 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.

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 7.2 Exclusion Criteria	[redacted]	[redacted]

Signature Page for TAK-062-2001 Protocol Amend 5 2023-NOV-16
Title: Amendment 5 to A Phase 2, Randomized, Double-Blind, Placebo-Controlled, D

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