Clinical Study Protocol

Protocol Title: **A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of PRV-015 in Adult Patients with Non-Responsive Celiac Disease as an Adjunct to a Gluten-free Diet**

Protocol Number: PRV-015-002b

Version Number: 3.0

Compound: PRV-015

Study Phase: 2b

Short Title: Phase 2b Study of PRV-015 in Gluten-free Diet Non-responsive Celiac Disease

Acronym: PROACTIVE (PROvention-Amgen Celiac protecTIVE study)

Sponsor Name: Provention Bio, Inc.

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Sponsor Signatory:

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24 March 2022

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Date

VP, Clinical Development

Provention Bio, Inc.

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In-Text Figures

Summary of Changes

Protocol version 2.0 to 3.0

Protocol PRV-015-002b version 2.0 (approved 01 March 2021) was amended to version 3.0 (approved 24 March 2022). Substantive changes to the previous version of the protocol are listed in the table below along with rationales. All changes are clearly identified in the track-changes version of the amendment.

Section	Rationale for change	Original Text	Revised Text
1.1, 4.1, 5.1 #8	The level of tTG and DGP antibodies for study inclusion is revised from <2.0 to <3.0 times the cutoff value for positivity. This minor change will slightly expand the patient base for enrollment, adding potentially more symptomatic patients, without altering the target patient population. Low positive tTG titers may help identify subjects with continued inadvertent exposure to gluten as a possible cause of their symptoms. The allowable level, <3.0 times the cutoff value for positivity, is still well below the typical levels seen in celiac patients not on a GFD, which can be >10 times the cutoff value for positivity at diagnosis.	8. Subjects must have detectable (above the lower limit of detection) serum celiac-related antibodies (at least one of anti-tTG IgA/IgG or DGP IgA/IgG). However, the titer in each assay must be below ~~2.0~~ times the diagnostic cut-off value for positivity of the assay in order to confirm that the subject is trying to adhere to their GFD.	8. Subjects must have detectable (above the lower limit of detection) serum celiac-related antibodies (at least one of anti-tTG IgA/IgG or DGP IgA/IgG). However, the titer in each assay must be below <u>3.0</u> times the diagnostic cut-off value for positivity of the assay in order to confirm that the subject is trying to adhere to their GFD.
1.1, 4.1, 9.2	Although a cap of enrollment of subjects with VH:CD≥2 was initially instituted to limit the number of	Enrollment of subjects with ~~VH:CD ≥2~~ will be capped at ~~32~~ subjects,	Enrollment of subjects with <u>Marsh score of 0 or 1</u> will be capped at

Section	Rationale for change	Original Text	Revised Text
	subjects with normal biopsies, which could affect the ability to detect improvements in histological outcomes, this criterion is revised to capping enrollment of subjects with Marsh score 0 or 1, which incorporates both VH:CD and IELs. The Marsh score better reflects the overall histological architecture, and changes from baseline in both VH:CD and IELs will be analyzed. A cap of 72 subjects, or approximately 33% of the planned total number of randomized subjects, will still limit those with normal biopsies but allow for a broader inspection of small bowel architecture using both VH:CD and/or IELs, thereby broadening subject participation.	although fewer than ~~32~~ may be enrolled.	approximately 72 subjects, although fewer than 72 may be enrolled.
5.2	The exclusion of IgA deficiency was originally instituted because of concerns for the effects of COVID-19 on celiac disease at the time of protocol development. Because of the widespread availability of the COVID-19 vaccines and accumulated data that demonstrate no increased risks to celiac patients	~~4. Selective IgA deficiency, defined as having undetectable levels of serum IgA.~~	(Original text removed)

Section	Rationale for change	Original Text	Revised Text
	from COVID-19 infection, this exclusion criterion is removed.		
8.4.1	The planned method for the analysis of delayed TEAEs in subjects who discontinue study treatment is removed and deferred to the Statistical Analysis Plan (SAP).	~~For subjects who discontinue treatment but remain in the study for continued assessments, TEAEs occurring less than 105 days from the last dose of study drug will be assigned to their study treatment. TEAEs reported more than 105 days after the last received dose will be assigned to placebo.~~	(Original text removed)

Protocol version 1.0 to 2.0

Protocol PRV-015-002b version 1.0 (approved 29 April 2020) was amended to version 2.0 (approved 01 March 2021). Substantive changes to the previous version of the protocol are listed in the table below along with rationales. In addition, minor corrections and administrative/editorial changes and clarifications have been made throughout the document. All changes are clearly identified in the track-changes version of the amendment.

Section	**Rationale for change**	**Original Text**	**Revised Text**
1.1, 4.1	Correction	Enrollment of subjects with VH:CD >2 will be capped at 32 subjects, although fewer than 32 may be enrolled.	Enrollment of subjects with VH:CD ≥2 will be capped at 32 subjects, although fewer than 32 may be enrolled.
1.1, 4.1, 8.2.1	Administrative		(The copyright of the CeD PRO [2015] is held by 9 Meters Biopharma and was formerly held by Alba Therapeutics Corporation. The CeD PRO is used with permission.)
1.3, 8.1	The antibody tests on the Day -14 visit (Visit -2) are removed to avoid any delay for the Day 0 visit and the start of study treatment.	See table	See table
1.3, 8.2.9	All urine samples will be collected at each visit.	Footnote 7. Stool gluten samples will be collected by the subject the day before each scheduled visit or during the visit (with a window of 3 days before or after the visit). Urine gluten samples will be collected ~~and~~	Footnote 7. Stool gluten samples will be collected by the subject the day before each scheduled visit or during the visit (with a window of 3 days before or after the visit). Urine gluten samples will be collected at the time of the office visit.

Section	Rationale for change	Original Text	Revised Text
		~~frozen by the subject either before or~~ at the time of the office visit.	
1.1, 4.1, 5.1 #8	The maximum levels of tTG and DGP antibodies for inclusion is revised from 1.5 to 2.0 times the cutoff value for positivity. This minor change will slightly expand the patient base for enrollment in this study, adding potentially more symptomatic patients without altering the target patient population in screening, as low positive titers help identify those subjects with potential continued inadvertent exposure to gluten as a potential cause of their symptoms. The change from 1.5 to 2.0 times is still well below the typical values seen without a GFD, as antibodies at diagnosis can be 10 times (or higher) the cutoff value for positivity.	8. Subjects must have detectable (above the lower limit of detection) serum celiac-related antibodies (at least one of anti-tTG IgA/IgG or DGP IgA/IgG). However, the titer in each assay must be below ~~1.5~~ times the diagnostic cut-off value for positivity of the assay in order to confirm that the subject is trying to adhere to their GFD.	8. Subjects must have detectable (above the lower limit of detection) serum celiac-related antibodies (at least one of anti-tTG IgA/IgG or DGP IgA/IgG). However, the titer in each assay must be below <u>2.0</u> times the diagnostic cut-off value for positivity of the assay in order to confirm that the subject is trying to adhere to their GFD.
1.1, 9.5	The DMC member composition is updated, as additional member(s) may be included to better assess available data during the study.	~~An internal DMC will consist of a Physician Chair, Physician Member, and an independent Statistician separate from the study team.~~	<u>An internal DMC will be set up to periodically evaluate trial-related data. The DMC will consist of at least 3 independent members not affiliated with the study. It will be chaired by a physician, and other</u>

Section	Rationale for change	Original Text	Revised Text
		Complete guidelines ~~and~~ evaluation criteria will be documented in a DMC Charter.	members will include at least 1 physician and 1 statistician. Complete guidelines, evaluation criteria, and other organizational and operational aspects will be documented in a DMC Charter.
1.3	The window for the baseline endoscopy is increased to 12 days prior to Visit 2 to improve scheduling feasibility.	Footnote 12. The baseline EGD and biopsy can be performed within ~~7~~ days before Visit 2.	Footnote 12. The baseline EGD and biopsy can be performed within 12 days before Visit 2.
5.1 #9, 8.8	Wording is updated to allow the inclusion of patients with less common HLA types associated with celiac disease.	9. Subjects must have human leukocyte antigen DQ (HLA-DQ) typing consistent with celiac disease (DQ2 and/or DQ8) obtained before the baseline biopsy. HLA-DQ typing information supplied as part of the subject medical record is acceptable.	9. Subjects must have human leukocyte antigen DQ (HLA-DQ) typing consistent with known celiac disease alleles (typically DQ2 and/or DQ8) obtained before the baseline biopsy. HLA-DQ typing information supplied as part of the subject medical record is acceptable.
5.4	To clarify the consenting procedures for subjects undergoing rescreening.	Randomization failures will not be rescreened.	Subjects who are rescreened should be reconsented at the time of the rescreening. Subjects who have entered the run-in period or were randomization failures will not be rescreened.

Section	Rationale for change	Original Text	Revised Text
8.1	Correction to include hemoglobin A1C at visits designated in the Schedule of Activities		(Visits 1, 5, 7, 9, 11, 13, 15, and 16) • HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
8.2.7	Correction and clarification.	At each time point specified in the SoA (Section 1.3), at a minimum, 6 ~~fragments~~ or specimens of small-bowel tissue will be taken from ~~the duodenal bulb and~~ the second part of the duodenum distal to the ampulla (duodenum D2) by EGD and forceps biopsy. ~~Biopsies should be done in the duodenum while avoiding ulcerative lesions.~~ 1. ~~The first 4 specimens collected will be fixed in a fixative such as PaxGene or 10% formalin (see Study Manual). One of the specimens may be fixed in formalin at the site for standard pathology (if conducted, the information will not be captured in the study). Three of the specimens will be shipped to the central lab to be embedded in paraffin wax after orientation.~~ The Central Pathologist, blinded to treatment assignment, will assess villus height (VH, in micrometers) and crypt depth (CD, in	At each time point specified in the SoA (Section 1.3), at a minimum, 6 biopsies or specimens of small-bowel tissue will be taken from the second part of the duodenum distal to the ampulla (duodenum D2) by EGD and endoscopic forceps biopsy. Ulcerative lesions should be avoided for all biopsies. 1. All 6 specimens will be fixed in PAXgene at the site (see Central Laboratory Manual) and shipped to the Central Pathologist. 2. The Central Pathologist, blinded to treatment assignment, will assess villus height (VH, in micrometers) and crypt depth (CD, in micrometers) and their ratio, VH:CD, using 4 specimens. 3. Two specimens will be placed in a messenger ribonucleic acid (mRNA) preservative for future mRNA analysis of inflammatory pathways (e.g., expression analysis of IL-15-

Section	Rationale for change	Original Text	Revised Text
		micrometers) and their ratio, VH:CD. … ~~2. The next two~~ specimens will be placed in a messenger ribonucleic acid (mRNA) preservative for future mRNA analysis of inflammatory pathways (e.g., expression analysis of IL-15-related pathways to potentially identify predictive biomarkers of response to PRV-015).	related pathways to potentially identify predictive biomarkers of response to PRV-015).
9.4.1	Correction	For the CeD PRO scores, baseline value ~~is averaged over~~ the 4-week placebo run-in period.	For the CeD PRO Abdominal domain scores, baseline value will be the average of scores over the last week of the 4-week placebo run-in period immediately before randomization.
9.4.4	Clarification	Additionally, ~~a binary outcome~~ will be derived, in which subjects are categorized as having worsening scores from baseline ~~and those with no change or improvement~~. The Cochran–Mantel–Haenszel test (CMH) stratified by baseline median Marsh-Oberhuber score will be used to assess differences between active	Additionally, categorical outcomes will be derived, in which subjects are categorized as having worsening scores, no change, or improvement from baseline. The Cochran–Mantel–Haenszel test (CMH) stratified by baseline median Marsh-Oberhuber score will be used to assess differences between active and

Section	Rationale for change	Original Text	Revised Text
		and placebo treatments in ~~this binary outcome~~.	placebo treatments in these categorical outcomes.
10.1.3	Administrative	Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets local regulatory and/or IRB/IEC requirements.	Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign and date a statement of informed consent that meets local regulatory and/or IRB/IEC requirements.
10.2.4	Clarification of procedures for SAE reporting	See text	See text

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of PRV-015 in Adult Patients with Non-Responsive Celiac Disease as an Adjunct to a Gluten-free Diet

Short Title: Phase 2b Study of PRV-015 in Gluten-free Diet Non-responsive Celiac Disease

Rationale:

Non-responsive celiac disease (NRCD) can be defined as persistent symptoms, signs, or laboratory abnormalities typical of celiac disease despite at least 6-12 months of treatment with a gluten-free diet (GFD) (Rubio-Tapia 2013). PRV-015 (also known as AMG 714), a monoclonal antibody (mAb) that blocks interleukin 15 (IL-15), has been shown to reduce intestinal inflammation and improve clinical symptoms induced by gluten consumption in celiac disease. PRV-015 may be effective as an adjunctive treatment to a GFD in NRCD patients.

Objectives and Endpoints:

Objective	Endpoint/Estimand
Primary	
• To assess the efficacy of PRV-015 in attenuating the symptoms of celiac disease in adult patients with NRCD as measured by the Abdominal Symptoms domain of the Celiac Disease Patient-Reported Outcome (CeD PRO) questionnaire	Endpoint: • Absolute change from baseline through Week 24 in abdominal symptoms as measured by the Abdominal Symptoms domain of the CeD PRO questionnaire Estimand: • The primary estimand is the difference in the overall mean values (averaged across 24 weeks) of each of the 3 PRV-015 treatment groups compared with placebo of the change from baseline in the Abdominal Symptoms domain of the CeD PRO questionnaire in the target population, regardless of compliance to study treatment or the occurrence of intercurrent events.

Objective	Endpoint/Estimand
Secondary	
• To assess the effect of treatment with PRV-015 on other measures of disease activity • To assess the safety, tolerability, and pharmacokinetics (PK) of PRV-015 when administered to adult patients with NRCD.	Secondary efficacy endpoints: • Absolute change from baseline through Week 24 in the Diarrhea and Loose Stool domain of the CeD PRO • Absolute change from baseline through Week 24 in gastrointestinal (GI) symptoms as assessed by the Total GI score (comprising the Abdominal Symptoms domain, the Diarrhea and Loose Stool domain, and the Nausea item) of the CeD PRO • Absolute change from baseline to Week 24 in small intestinal mucosal inflammation, as measured by intraepithelial lymphocyte (IEL) density using immunohistochemistry (IHC) Safety endpoints: • Adverse events (AEs): treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation, and treatment-emergent serious adverse events (SAEs) • Treatment-emergent adverse events of special interest (AESIs) • Potentially clinically important (PCI) changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs (blood pressure [BP], heart rate, temperature, respiratory rate), and weight • Immunogenicity, as assessed by the presence of anti-PRV-015 antibodies PK endpoint: • Serum PRV-015 trough concentrations (C_{min})

See Section 9.4.2 for a description of the primary endpoint analysis.

Overall Design:

Protocol PRV-015-002b is a Phase 2b, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of PRV-015 in adult patients with NRCD who are on a GFD.

After signing informed consent form (ICF), subjects will undergo screening assessments for the study in a screening period of up to 28 days before Visit 1. The screening assessments will include the collection of demographics, medical history, and past record of the diagnosis of celiac disease if available. Subjects should demonstrate 1) attempted adherence to a GFD, confirmed by a lack of strong serological positivity (<3.0 × cutoff value for positivity), and 2) exposure to gluten contamination by presenting with detectable serology (above the lower limit of quantitation).

After initial screening, potentially eligible subjects will enter a single-blind, placebo run-in period for 4 weeks, starting at Visit 1. During the run-in period, all subjects will receive subcutaneous (SC) injections of placebo every 2 weeks (q2w), at Visit 1 and Visit 2, in a single-blind fashion, in which the Investigator is aware of the treatment administered but the subjects are not. Subjects will be asked to maintain their current GFD through the entire study and to complete the daily electronic diary (eDiary) for CeD PRO questionnaire as well as a stool frequency question (stools of Type 6 or 7 on BSFS). (The copyright of the CeD PRO [2015] is held by 9 Meters Biopharma and was formerly held by Alba Therapeutics Corporation. The CeD PRO is used with permission.) A baseline upper esophagogastroduodenoscopy (EGD) and biopsy will be conducted during the single-blind run-in period. The results will be used to obtain the villous height-to-crypt depth ratio (VH:CD) for randomization stratification.

At the end of the 4-week single-blind, placebo run-in period, subjects will return to the study site for Visit 3 (Week 0/Day 1) and be re-evaluated for inclusion/exclusion criteria. Those who meet the entry criteria at this time will enter the 24-week double-blind treatment period (from Visit 3 to Visit 15). At the same visit, eligible subjects will be randomized in a 1:1:1:1 ratio to receive 100 mg, 300 mg, or 600 mg PRV-015, or matching placebo, subcutaneously (SC) every 2 weeks (q2w). Randomization will be stratified by VH:CD of <2 or ≥2 and by the CeD PRO Abdominal Symptoms domain score of <3 or ≥3 at baseline using the average of the Abdominal Symptoms domain scores over the last week of the placebo run-in period immediately before randomization. Enrollment of subjects with Marsh score of 0 or 1 will be capped at approximately 72 subjects, although fewer than 72 may be enrolled.

The study drug (1 of the 3 doses of PRV-015 or placebo) will be administered SC q2w in the double-blind treatment period through Visit 14. Each dose will be administered in a double-blind fashion. The subjects' adherence to GFD will be assessed retrospectively throughout the study using the stool and urine gluten tests based on the G12 antibody to interpret possible dietary changes or transgressions. Results will not be communicated to the subjects, who will be instructed to continue their baseline dietary habits throughout the study.

Subjects will be assessed for efficacy and safety throughout the study, as indicated in the Schedule of Activities (SoA) (Section 1.3). Clinical assessments occur from Visit 3 through Visit 16. Safety is also assessed at each on-site visit through the end-of-study visit (Visit 16), which takes place 6 weeks after the last planned dose of the study drug.

Randomized subjects will undergo a second EGD and biopsy at the end of the 24-week treatment period, within 7 days of Visit 15 in order to assess changes from baseline in IELs and VH:CD.

Visits 6, 8, 10, and 12 may be conducted either at the site or remotely by certified mobile personnel per the Investigator's decision.

All subjects enrolled in the study will complete the daily eDiary for CeD PRO (at the end of the subject's daily activities, when no more food will be consumed) and for the stool frequency question from Visit 1 through the end of the study at Visit 16, which will encompass the single-blind placebo run-in and the double-blind treatment period and a safety follow-up period.

Safety assessments include clinical laboratory tests, vital signs, and AE assessments. Subjects may undergo unscheduled visits if needed (e.g., for safety reasons).

Disclosure Statement: This is a parallel-group treatment study with 4 treatment groups double blinded to subjects, investigators, and sponsor, preceded by a single-blind placebo run-in period.

Number of Subjects:

Approximately 220 subjects will be randomized (approximately 55 subjects per group). Subjects will be stratified by normal or abnormal VH:CD (i.e., ≥2 or <2) and by the CeD PRO Abdominal Symptoms domain score of <3 or ≥3 at baseline, using the average of the Abdominal Symptoms domain scores over the last week of the placebo run-in period immediately preceding randomization. The number of enrolled subjects with Marsh score of 0 or 1 will be capped at approximately 72. Withdrawn subjects will not be replaced.

A sample size of 50 evaluable subjects within each treatment group would provide approximately 80% power to detect a 0.40 difference between placebo and any given active treatment group at the two-sided, 0.05 level of significance during the 24-week double-blind treatment period in the primary endpoint. See Section 9.2 for details.

Treatment Groups and Duration:

After the single-blind placebo run-in phase, subjects will be randomized to one of the 4 treatment groups in a ratio of 1:1:1:1 as follows:

- PRV-015 100 mg q2w
- PRV-015 300 mg q2w
- PRV-015 600 mg q2w
- Placebo q2w

The duration of study participation for each subject is approximately 9 months, including ≤4 weeks of screening period, 4 weeks of placebo run-in period, 24 weeks of double-blind treatment period, and 4 weeks of final safety follow-up period.

Internal Data Monitoring Committee (DMC):

An internal DMC will be set up to periodically evaluate trial-related data. The DMC will consist of at least 3 independent members not affiliated with the study. It will be chaired by a physician, and other members will include at least 1 physician and 1 statistician.

The DMC will receive blinded and unblinded data before each meeting. The DMC will meet at least quarterly. The DMC may also hold emergency meetings in the event of death regardless of relatedness, life-threatening events possibly related to study drug, or anaphylaxis to advise on continued study conduct. Relevant medical literature may also be reviewed by the committee.

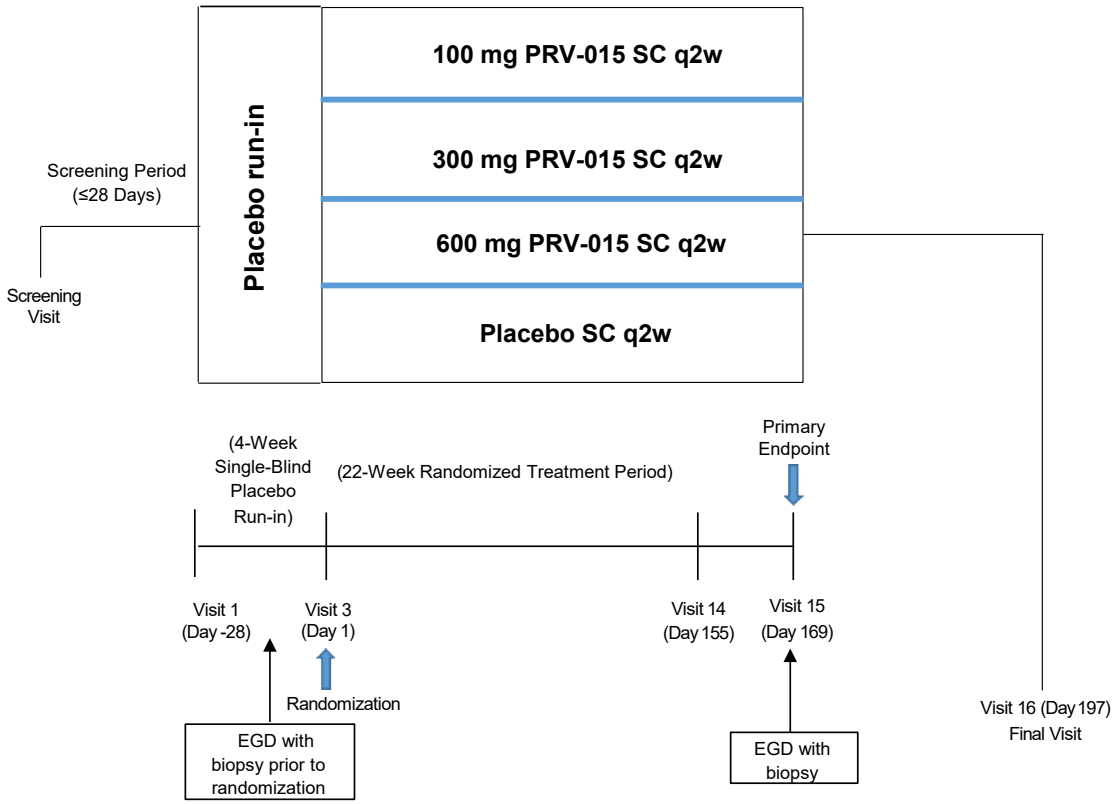
Complete guidelines, evaluation criteria, and other organizational and operational aspects will be documented in a DMC Charter.

An additional series of Safety Meetings will be held between the study team, including the Sponsor Safety Physician, and Amgen, the holder of the global safety database.

1.2. Schema

A schema of the study procedures is presented in Figure 1.

Figure 1 Study Schema



Abbreviations: EGD=esophagogastroduodenoscopy, q2w=every 2 weeks, SC=subcutaneous.

1.3. Schedule of Activities (SoA)

	Screening (≤28 Days)	Single-Blind Run-in Period		Double-Blind Randomized Treatment Period													Follow-up Visit
Visit #	**Screen[1]**	**1**	**2**	**3**	**4**	**5**	**6[2]**	**7**	**8[2]**	**9**	**10[2]**	**11**	**12[2]**	**13**	**14**	**15/ Early Term**	**16**
Week	**-8**	**-4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**28**
Day	**-56**	**-28**	**-14**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**197**
Window (Days)			±2	+2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±7
Study Procedures																	
Informed consent	X																
Demographics	X																
Medical history	X																
Physical examination[3]	X	X	X	X	X	X		X		X		X		X		X	X
Weight	X	X	X	X	X	X		X		X		X		X		X	X
Height	X																
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X																
Blood and urine samples for clinical lab tests[5]	X[6]	X		X		X		X		X		X		X		X	X
H. pylori stool test	X																
Blood tests for ferritin, iron, TIBC, vitamins D, B12, folate				X						X						X	
Serum pregnancy test (WOCBP)	X																
LH/FSH (non-WOCBP)	X																
Urine pregnancy test (all WOCBP)		X	X	X		X		X		X		X		X		X	X
Stool and urine gluten test[7]		X	X	X	X	X		X		X		X		X		X	X

	Screening (≤28 Days)	Single-Blind Run-in Period		Double-Blind Randomized Treatment Period													Follow-up Visit
Visit #	**Screen[1]**	**1**	**2**	**3**	**4**	**5**	**6[2]**	**7**	**8[2]**	**9**	**10[2]**	**11**	**12[2]**	**13**	**14**	**15/ Early Term**	**16**
Week	**-8**	**-4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**28**
Day	**-56**	**-28**	**-14**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**197**
Window (Days)			**±2**	**+2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**
Randomization				X													
Serum IgA test	X																
Serum for PK[8]				X	X	X		X		X		X		X	X	X	X
Serum for ADA[8]				X	X	X				X					X	X	X
Anti-tTG and anti-DGP antibodies[9]	X			X		X		X		X		X		X		X	X
Serum for biomarkers[10]				X		X		X		X		X		X		X	X
Eligibility confirmation	X			X													
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		X[11]	X[11]	X	X	X	X	X	X	X	X	X	X	X	X		
EGD and biopsy			X[12]													X[13]	
Stool frequency question[14]		<----------														---------->	
CeD PRO[15]		<----------														---------->	
ICDSQ				X						X						X	
EQ-5D-5L				X						X						X	
Weekly diet stability questions		<----------														---------->	
GSRS	X																
IGA		X		X	X	X		X		X		X		X		X	X
PGIC[16]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIS[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of adverse events[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA=anti-drug antibody; BP=blood pressure; BSFS=Bristol Stool Form Scale; CeD PRO=Celiac Disease Patient Reported Outcome; DGP=deamidated gliadin peptide; ECG=electrocardiogram; EGD=esophagogastroduodenoscopy; Early Term=early termination; FSH=follicle-stimulating hormone; GSRS=Gastrointestinal Symptom Rating Scale; HbA1C=hemoglobin A1C; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA=human leukocyte antigen; IGA=Investigator Global Assessment; LH=luteinizing hormone; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; QoL=quality of life; TIBC=total iron binding capacity; tTG=tissue transglutaminase; WOCBP=women of childbearing potential, non-WOCBP=women not of childbearing potential.

1. Testing for COVID-19 infection (including viral RNA testing for acute infection and/or antibody testing for past exposure) may be conducted if appropriate.
2. Visits 6, 8, 10, and 12 may be conducted remotely by certified mobile healthcare personnel per Investigator's decision.
3. A complete physical examination is required at screening, Visit 1, Visit 15, and Visit 16. At other visits, the physical examinations are symptom directed.
4. Vital signs (including temperature, BP, heart rate, and respiratory rate) will be measured prior to each study drug administration. Vital signs will be taken again 30 minutes after study drug administration.
5. Blood and urine samples will be collected for hematology, chemistry, and urinalysis. In addition, HbA1c should be measured in those subjects with diagnosis of Type 1 or Type 2 diabetes only. If glucose is detected in the urine, HbA1c should be tested and the subject should receive clinical evaluation for diabetes per standard of care.
6. The screening blood samples include HIV, HBV, HCV, and IGRA tests. In addition, a test for HLA DQ2 and/or DQ8 typing will be performed if a previous report is not supplied.
7. Stool gluten samples will be collected by the subject the day before each scheduled visit or during the visit (with a window of 3 days before or after the visit). Urine gluten samples will be collected at the time of the office visit.
8. Blood samples for PK and ADA analyses should be collected before study drug administration (baseline) and at each visit before dosing (trough). The exact time and date of sample collection must be recorded. ADA analysis includes neutralizing antibodies (NAb).
9. The anti-tTG and anti-DGP antibody tests at the screening visit will include both IgA and IgG. At all other visits, only anti-tTG IgA and anti-DGP IgA will be tested.
10. Blood samples for biomarker analyses should be taken prior to study drug administration. The time and date of these samples must be accurately recorded.
11. The study drug administered at Visits 1 and 2 (single-blind run-in period) is placebo for all subjects.
12. The baseline EGD and biopsy can be performed within 12 days before Visit 2.
13. The final EGD and biopsy can be collected within 7 days before Visit 15. A final or early termination EGD and biopsy are required for all subjects. Subjects with early termination should undergo the EGD and biopsy unless a medical condition precludes it, at the Investigator's discretion.
14. Subjects are required to answer the stool frequency question (stools of Type 6 or 7 on BSFS) daily before bedtime in the eDiary.
15. The CeD PRO is captured daily in the eDiary after the last meal of the day before the subject goes to bed.
16. Subjects are instructed to record PGIC and PGIS every other week in the eDiary.
17. Treatment-emergent adverse events are collected from the first dose of the post-randomization study drug administration (Visit 3) through the final visit. Between signing the informed consent form and the first dose of study drug (including the single-blind run-in period), only AEs related to study procedures and SAEs will be recorded.

2. Introduction

PRV-015, also known as AMG 714, is a monoclonal antibody (mAb) targeting interleukin (IL) 15 (IL-15). It is being developed as an adjunct to a gluten-free diet (GFD) for the treatment of non-responsive celiac disease (NRCD).

2.1. Study Rationale

Approximately 50% of patients with celiac disease have continued symptoms despite at least 12 months of treatment with a GFD. NRCD is defined by the American College of Gastroenterology (ACG) as persistent symptoms, signs, or laboratory abnormalities typical of celiac disease despite at least 6-12 months of treatment with a GFD (Rubio-Tapia 2013).

PRV-015, a mAb that blocks IL-15, has been shown to reduce intestinal inflammation and improve clinical symptoms induced by gluten consumption in a previous Phase 2a gluten-challenge study in patients with celiac disease. PRV-015 may be effective as an adjunctive treatment to GFD in NRCD patients.

2.2. Background

Celiac disease is a systemic autoimmune disease triggered by gluten consumption in genetically susceptible individuals (Green 2007). Approximately 1% of the European and North American population is affected by celiac disease, although many patients remain undiagnosed due to insufficient awareness and highly variable presentation of the disease. Currently, the only available management of celiac disease is lifelong total avoidance of gluten, i.e., a GFD. While simple in theory, maintaining a strict GFD is extremely difficult in practice because of occasional dietary transgressions and gluten contamination in foods purported to be gluten free. It has been estimated that half or more of all diagnosed patients who are following a GFD continue to have some disease activity, since as little as 50 mg/day of gluten exposure may trigger immune activation and mucosal damage (Gibert 2006, Lee 2003, Cranney 2007, Hopper 2007, Midhagen 2003, Moreno 2017). There are significant unmet medical needs in patients with NRCD.

The pro-inflammatory cytokine IL-15 has been identified as a major mediator in the pathophysiology of celiac disease (Gianfrani 2005, Meresse 2012). IL-15 is produced in the small intestine by antigen-presenting cells and epithelial cells and has been shown to be an essential, nonredundant factor for the activation and proliferation of intraepithelial lymphocytes (IELs). The IELs, primarily CD8+ cells, have been shown to destroy intestinal epithelial cells and cause the villous atrophy that is characteristic of celiac disease (Korneychuk 2014; Abadie 2014). Numerous genetic variants in the IL-15 and IL-15 receptor α (IL-15Rα) genes have been associated with IL-15 protein expression and the risk of celiac disease (Escudero-Hernandez 2017). In addition, IL-15 renders effector T cells resistant to inhibition by regulatory T cells, thus promoting the loss of tolerance to food antigens (Korneychuk 2014, Abadie 2014, DePaolo 2011). Further, IL-15 induces an increase in enterocyte apoptosis, which in turn correlates with mucosal damage and villous atrophy (Di Sabatino 2006).

PRV-015, a fully human immunoglobulin (IgG1κ) mAb, binds to and inhibits the function of IL-15 in all of its presentations (cis, trans, soluble IL-15 bound to IL-15Rα), and blocks IL-15-induced T-cell proliferation (Villadsen 2003). It has also demonstrated dose-dependent inhibition of IL-15-induced tumor necrosis factor alpha (TNF-α) production. Thus, PRV-015 is a plausible candidate for the treatment of celiac disease.

PRV-015 was previously tested in clinical trials for efficacy and safety in patients with rheumatoid arthritis (RA) (Baslund 2005, McInnes 2006), refractory celiac disease Type II (RCD-II) (Cellier 2019), and psoriasis (Lebrec 2013) and has shown acceptable safety and tolerability in all studies. Proof of concept was achieved in RA and RCD-II, while PRV-015 showed no efficacy in psoriasis.

A randomized, double-blind, placebo-controlled Phase 2a study in celiac disease was conducted, in which patients who were well controlled on their GFD were given a gluten challenge (2 to 4 g daily) while being treated with either PRV-015 (150 mg or 300 mg subcutaneous [SC] injection) or placebo (Lähdeaho 2019). A small number of patients in this study had NRCD, as demonstrated by presence of gastrointestinal mucosal damage at baseline, and did not undergo gluten challenge. After 12 weeks of study treatment, the primary endpoint, change from baseline to Week 12 in the villous height-versus-crypt depth ratio (VH:CD), was not met in the comparisons between placebo and either of the PRV-015 doses. However, patients in the PRV-015 300 mg group showed better outcomes in the endpoints of change from baseline in IEL density, Celiac Disease Patient-Reported Outcome (CeD PRO) score, the proportion of patients who reported diarrhea (defined as stools of Type 6 or 7 on the Bristol Stool Form Scale [BSFS]), and Physician Global Assessment (Lähdeaho 2019). Subjects who did not receive gluten challenge also experienced nominal symptom reduction, albeit the sample size was too small for statistical analyses. The findings indicate that PRV-015 can attenuate the inflammatory effects and symptoms induced by gluten challenge. The mixed results in histology and other endpoints in this study may be due to limitations in the sample size, treatment duration and dosage administered. Hence, the current larger Phase 2b dose-ranging study will investigate the effects of PRV-015 with a longer duration of treatment and broader range of doses (without gluten challenge) in patients exposed to contaminating gluten exposure, i.e., in symptomatic NRCD patients as an adjunct to a GFD.

2.3. Benefit/Risk Assessment

PRV-015 (also known as AMG 714) has been studied to date in over 250 subjects, including healthy volunteers and adult patients with psoriasis, RA, celiac disease (with gluten challenge), and RCD-II. The doses studied were 150 mg and 300 mg SC every 2 weeks (q2w) for 12 weeks in the celiac disease study and 8 mg/kg intravenous (IV) weekly for 3 doses followed by q2w for 4 doses (total treatment duration 10 weeks) in the RCD-II study.

Collectively, the prior safety data from earlier studies suggest an acceptable safety profile with the following identified adverse reactions, which, to date, have been mild and transient in nature:

- Injection site reaction
- Infusion site pain
- Rash
- Eczema

Due to the common occurrence of injection site reactions (up to 52% in subjects receiving 300 mg PRV-015 in the CELIM-NRCD-001 study), post-injection observation for at least 1 hour is required at all dosing visits.

See the Investigator Brochure (IB) Core Safety Information for further details of the safety of PRV-015 injection.

The patients to be enrolled in this Phase 2b study will have followed GFD for at least 12 months and, in spite of their best efforts, will have residual symptoms, evidence of anti-gluten and/or auto-antibody formation, and likely continued intestinal inflammation and damage. PRV-015 may relieve symptoms and potentially reduce intestinal inflammation. The safety profile to date suggests that the risks associated with PRV-015 are mild and transient, and predominantly injection site reactions.

In summary, PRV-015 provides an opportunity for an innovative approach to provide clinical benefits to patients with NRCD at a relatively low risk.

3. Objectives and Endpoints

Objective	Endpoint/Estimand
Primary	
• To assess the efficacy of PRV-015 in attenuating the symptoms of celiac disease in adult patients with NRCD as measured by the Abdominal Symptoms domain of the Celiac Disease Patient-Reported Outcome (CeD PRO) questionnaire	Endpoint: • Absolute change from baseline through Week 24 in abdominal symptoms as measured by the Abdominal Symptoms domain of the CeD PRO questionnaire Estimand: • The primary estimand is the difference in the overall mean values (averaged across 24 weeks) of each of the 3 PRV-015 treatment groups compared with placebo of the change from baseline in the Abdominal Symptoms domain of the CeD PRO questionnaire in the target population, regardless of compliance to study treatment or the occurrence of intercurrent events.
Secondary	
• To assess the effect of treatment with PRV-015 on other measures of disease activity • To assess the safety, tolerability, and pharmacokinetics (PK) of PRV-015 when administered to adult patients with NRCD.	Secondary efficacy endpoints: • Absolute change from baseline through Week 24 in the Diarrhea and Loose Stool domain of the CeD PRO • Absolute change from baseline through Week 24 in gastrointestinal (GI) symptoms as assessed by the Total GI score (comprising the Abdominal Symptoms domain, the Diarrhea and Loose Stool domain, and the Nausea item) of the CeD PRO • Absolute change from baseline to Week 24 in small intestinal mucosal inflammation, as measured by

Objective	Endpoint/Estimand
	intraepithelial lymphocyte (IEL) density using immunohistochemistry (IHC) Safety endpoints: • Adverse events (AEs): treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation, and treatment-emergent serious adverse events (SAEs) • Treatment-emergent adverse events of special interest (AESIs) • Potentially clinically important (PCI) changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs (blood pressure [BP], heart rate, temperature, respiratory rate), and weight • Immunogenicity, as assessed by the presence of anti-PRV-015 antibodies PK endpoint: • Serum PRV-015 trough concentrations (C_{min})
Tertiary/Exploratory	
[redacted]	[redacted]

Objective	Endpoint/Estimand
[redacted]	[redacted]

Objective	Endpoint/Estimand
	[redacted]

4. Study Design

4.1. Overall Design

Protocol PRV-015-002b is a Phase 2b, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of PRV-015 in adult patients with NRCD who are on a GFD.

After signing informed consent form (ICF), subjects will undergo screening assessments for the study in a screening period of up to 28 days before Visit 1. The screening assessments will include the collection of demographics, medical history, and past record of the diagnosis of celiac disease if available. Subjects should demonstrate 1) attempted adherence to a GFD, confirmed by a lack of strong serological positivity (<3.0 × cutoff value for positivity), and 2) exposure to gluten contamination by presenting with detectable serology (above the lower limit of quantitation).

After initial screening, potentially eligible subjects will enter a single-blind, placebo run-in period for 4 weeks, starting at Visit 1. During the run-in period, all subjects will receive subcutaneous (SC) injections of placebo every 2 weeks (q2w), at Visit 1 and Visit 2, in a single-blind fashion, in which the Investigator is aware of the treatment administered but the subjects are not. Subjects will be asked to maintain their current GFD through the entire study and to complete the daily electronic diary (eDiary) for CeD PRO questionnaire as well as a stool frequency question (stools of Type 6 or 7 on BSFS). (The copyright of the CeD PRO [2015] is held by 9 Meters Biopharma and was formerly held by Alba Therapeutics Corporation. The CeD PRO is used with permission.) A baseline upper esophagogastroduodenoscopy (EGD) and biopsy will be conducted during the single-blind run-in period. The results will be used to obtain the VH:CD for randomization stratification.

At the end of the 4-week single-blind, placebo run-in period, subjects will return to the study site for Visit 3 (Week 0/Day 1) and be re-evaluated for inclusion/exclusion criteria. Those who meet the entry criteria at this time will enter the 24-week double-blind treatment period (from Visit 3 to Visit 15). At the same visit, eligible subjects will be randomized in a 1:1:1:1 ratio to receive 100 mg, 300 mg, or 600 mg PRV-015, or matching placebo, subcutaneously (SC) every 2 weeks (q2w). Randomization will be stratified by VH:CD of <2 or ≥2 and by the CeD PRO Abdominal Symptoms domain score of <3 or ≥3 at baseline using the average of the Abdominal Symptoms domain scores over the last week of the placebo run-in period immediately before randomization. Enrollment of subjects with Marsh score of 0 or 1 will be capped at approximately 72 subjects, although fewer than 72 may be enrolled.

The study drug (1 of the 3 doses of PRV-015 or placebo) will be administered SC q2w in the double-blind treatment period through Visit 14. Each dose will be administered in a double-blind fashion. The subjects' adherence to GFD will be assessed retrospectively throughout the study using the stool and urine gluten tests based on the G12 antibody to interpret possible dietary changes or transgressions. Results will not be communicated to the subjects, who will be instructed to continue their baseline dietary habits throughout the study.

Subjects will be assessed for efficacy and safety throughout the study, as indicated in the Schedule of Activities (SoA) (Section 1.3). Clinical assessments occur from Visit 3 through Visit

16. Safety is also assessed at each on-site visit through the end-of-study visit (Visit 16), which takes place 6 weeks after the last planned dose of the study drug.

Randomized subjects will undergo a second EGD and biopsy at the end of the 24-week treatment period, within 7 days of Visit 15 in order to assess changes from baseline in IELs and VH:CD.

Visits 6, 8, 10, and 12 may be conducted either at the site or remotely by certified mobile personnel per the Investigator's decision.

All subjects enrolled in the study will complete the daily eDiary for CeD PRO (at the end of the subject's daily activities, when no more food will be consumed) and for the stool frequency question from Visit 1 through the end of the study at Visit 16, which will encompass the single-blind placebo run-in and the double-blind treatment period and a safety follow-up period.

Safety assessments include clinical laboratory tests, vital signs, and AE assessments. Subjects may undergo unscheduled visits if needed (e.g., for safety reasons).

An internal Data Monitoring Committee (DMC) will monitor the study conduct (see Section 9.5).

4.2. Scientific Rationale for Study Design

This study uses a randomized, double-blind, placebo-controlled, parallel-group design to evaluate the efficacy and safety of 3 dose regimens of PRV-015 in adult NRCD patients. This dose-ranging study design was chosen to separately compare the effects of each dose regimen and placebo and select a dose(s) for future development. The double-blind approach and the use of placebo (with matching appearance to the active treatment) are intended to minimize bias in the assessment and reporting of symptoms. Placebo is essential for demonstrating efficacy of a clinical symptom endpoint in the NRCD population, for which there are no approved pharmacologic therapies. Both groups will be receiving standard of care (GFD), and the study design will allow for a direct comparison to evaluate the effects of the active treatment.

There is a single-blind run-in period of 4-week placebo treatment before the start of the randomized, double-blind treatment period. This period will allow the selection of patients who are truly nonresponsive to their GFD and therefore in need of adjunctive treatment.

The primary efficacy endpoint, absolute change from baseline through Week 24 in the Abdominal Symptoms domain of CeD PRO, was chosen as a direct measure of changes in subjects' clinical symptoms. The CeD PRO is the only fully validated symptom endpoint in celiac disease. In previous studies, PRV-015 has been shown to reduce the GI inflammatory process and symptoms. Considering the multiorgan, nonspecific symptoms associated with celiac disease, the Abdominal Symptoms domain, which includes GI symptoms, is expected to be the most sensitive domain that best reflects the manifestations of active disease and where IL-15 blockade would most likely translate to beneficial clinical outcomes.

4.3. Justification for Dose

[redacted]

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study through Visit 16 (Week 28).

The primary completion date of the study is the date on which the last subject in the study provides final data for the primary efficacy assessment.

The end of the study is defined as the date of the last assessment or data collection for the last subject in the study.

5. Study Population

5.1. Inclusion Criteria

Subjects must fulfill all of the following criteria at screening and, if applicable, at randomization (Visit 3) to be eligible for participation:

1. Adult males or females 18 to 70 years of age, inclusive.
2. Subjects demonstrate willingness to participate in the study and to perform all required procedures as documented by signed informed consent.
3. Subjects must have a diagnosis of celiac disease by intestinal biopsy at least 12 months prior to screening as confirmed by medical records or written physician statement.
4. Subjects must have reported attempting to follow a GFD for at least the 12 consecutive months prior to screening and must be willing to maintain their current diet for the duration of study participation.
5. Subjects must have had at least one of the following symptoms at least once per week during the month before screening: diarrhea, loose stools, abdominal pain, abdominal cramping, bloating, or gas.
6. Subjects must have a Gastrointestinal Symptom Rating Scale, Celiac Disease portion (CeD-GSRS) score of >2 at the screening visit.
7. During the 4-week single-blind placebo run-in period, subjects must have a CeD PRO Abdominal Symptoms domain weekly average score ≥2.5 in at least 2 of the 4 weeks prior to the randomization visit (Visit 3) AND the CeD PRO Abdominal Symptom domain weekly average scores must not trend toward improvement from the initial weekly score (defined as continued improvement in weekly scores from week to week OR >50% improvement from the initial score).
8. Subjects must have detectable (above the lower limit of detection) serum celiac-related antibodies (at least one of anti-tTG IgA/IgG or DGP IgA/IgG). However, the titer in each assay must be below 3.0 times the diagnostic cut-off value for positivity of the assay in order to confirm that the subject is trying to adhere to their GFD.
9. Subjects must have human leukocyte antigen DQ (HLA-DQ) typing consistent with known celiac disease alleles (typically DQ2 and/or DQ8) obtained before the baseline biopsy. HLA-DQ typing information supplied as part of the subject medical record is acceptable.
10. Body weight between 35 and 120 kg, inclusive.
11. Female subjects must meet the following inclusion criteria:
    a. Women not of childbearing potential:

       Postmenopausal is defined as being >45 years of age with amenorrhea for at least 18 months) or >45 years of age with amenorrhea for at least 12 months and a confirmatory serum follicle-stimulating hormone (FSH) level >40 IU/L with luteinizing hormone (LH) level >40 IU/L in women not receiving hormone replacement therapy; permanently sterilized (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy). Note: tubal ligation is not considered permanent sterilization.

b. Women of childbearing potential (WOCBP):
    i. Must have a negative serum β-human chorionic gonadotropin (β-hCG) at screening and a negative urine pregnancy test at randomization.
    ii. Must practice a highly effective method of birth control (<1% failure rate) consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies (see Appendix 10.3).
    iii. Must agree to use highly effective methods of birth control throughout the study and for 3 months after receiving the last dose of study drug.
    iv. Must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 3 months after receiving the last dose of study drug.

12. Male subjects must meet the following criterion: A man who is sexually active with a woman of childbearing potential and has not had a vasectomy or otherwise surgically sterile must agree to highly effective birth control for their female partner and must use condoms with spermicide during sexual intercourse, and this must continue for 3 months after receiving the last dose of study drug. All men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria applies at either screening or, if applicable, at randomization (Visit 3):

1. Current diagnosis of any severe complication of celiac disease, such as RCD-I or RCD-II, enteropathy-associated T-cell lymphoma (EATL), ulcerative jejunitis, or GI perforation.
2. Diagnosis of any chronic, active GI disease other than celiac disease, such as active, untreated peptic ulcer, eosinophilic esophagitis, erosive esophagitis , ulcerative colitis or Crohn's disease, microscopic colitis, irritable bowel syndrome, small intestinal bacterial overgrowth, tropical sprue, or other GI and non-GI disorder or prior GI surgery that may, in the Investigator's opinion, interfere with the assessment of symptoms of abdominal pain, diarrhea, or other components of celiac disease.
3. Any known, symptomatic food allergy that, in the opinion of the Investigator, may interfere with the conduct or interpretation of the study.
4. Presence of any of the following related to infection:
    a. Active acute infection with flu-like symptoms such as fever, cough, or shortness of breath; or active infections requiring systemic (intravenous or intramuscular) treatment (antibiotics, antifungal, or antiviral).
    b. Active GI infection, including *H. pylori*.
    c. History of tuberculosis (TB) except for successful chemoprophylaxis for positive TB tests.
    d. Positive Interferon Gamma Release Assay (IGRA) test at screening. Subjects with potential false-positive tests may have the test repeated. If chest X-ray is also clear, they may be enrolled.

e. History of an opportunistic infection typical of those seen in immunocompromised patients (e.g., herpes zoster, systemic candida infection, or systemic fungal infection) within 3 years prior to screening.

5. Any of the following laboratory test abnormalities at screening or Visit 1 (Day -28):
   a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN).
   b. Hemoglobin <9 g/dL (<90 g/L in SI units).
   c. Platelet count <100,000 mm^3 (<100/L).
   d. White blood cell count <3,000 cells/mm^3 (<3.0 $\times 10^9$/L).
   e. Creatinine >1.5 mg/dL.
   f. Hemoglobin A1c (HbA1c) >9% (>90 mmol/mol) in subjects with a concurrent diagnosis of Type 1 or Type 2 diabetes.
6. Use of systemic immune suppressants (including systemic or GI topical steroids) during the screening or single-blind placebo run-in period.
7. Required use of a prohibited medication (see Section 6.5.1) during the screening or single-blind placebo run-in period.
8. Current diagnosis or recent history of cancer within the past 5 years, except successfully treated basal cell or squamous cell carcinoma, cervical carcinoma-in-situ, or early-stage prostate cancer.
9. Known or suspected exposure to COVID-19 infection in the 4 weeks before screening.
10. Administration of a live vaccine within 14 days prior to randomization and the first administration of study drug at Visit 3.
11. History or presence of any clinically significant disease that, in the opinion of the Investigator, may confound the subject's participation and follow-up in the clinical trial or put the subject at unnecessary risk, including but not limited to: uncontrolled hypertension (BP ≥180/110 mm/Hg), unstable angina, Class II congestive heart failure or major fluid overload, coronary angioplasty or myocardial infarction within the past 6 months, clinically significant arrhythmias or electrocardiogram (ECG) abnormalities, severe chronic pulmonary disease, or any renal, hematologic, GI, immunologic, dermatologic, neurologic, or psychiatric disease.
12. History of significant substance or alcohol abuse during the 12 months prior to screening as obtained by medical record and/or subject report.
13. Hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) positive test results.
14. Females who are pregnant or planning to become pregnant during the study period, or who are currently breastfeeding.
15. Participation in another investigational drug or device study or treatment with an investigational drug within 30 days or 5 half-lives, whichever is longer, prior to screening.
16. Any other reason that, in the opinion of the Investigator, may prevent the subject from safely participating in the study or complying with protocol requirements, including the endoscopies and biopsies.

5.3. Lifestyle Considerations

Subjects are required to maintain the same diet as they have been adhering to during the entire study.

Subjects are required to refrain from blood donation, illicit drug use (per applicable laws), and alcohol abuse (based on Investigator's judgment) throughout the duration of the study.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but do not enter the single-blind placebo run-in phase. Randomization failures are defined as those who enter the single-blind placebo run-in phase but do not meet the inclusion criteria or meet any exclusion criteria at Visit 3 and therefore are not randomized to a treatment group.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any screening SAE.

Individuals who are screen failures may be rescreened once. Rescreened subjects will be assigned the same subject number as for the initial screening. Subjects who are rescreened should be reconsented at the time of the rescreening. Subjects who have entered the run-in period or were randomization failures will not be rescreened.

6. Study Treatment

Study treatment is defined as any investigational product or placebo to be administered to a study subject according to the study protocol.

6.1. Study Drug Administered

At each visit, each subject will receive 4 injections for a total volume of 6 mL. Depending on the assigned treatment group, the amount of active PRV-015 and/or placebo injected will vary as outlined below to administer the desired dose while maintaining the double blind.

Name	PRV-015	Placebo
Type	Biologic	Protein-free solution
[redacted]		
Unit Dose Strength(s)	100 mg/mL with 2 mL deliverable volume in a 10 mL vial	N/A 1 ml placebo solution in 5 mL vials
Dosage Levels and Frequency	a. 100 mg q2w b. 300 mg q2w c. 600 mg q2w	Placebo q2w
Volume per Dose	a. 1 mL active × 1 syringe, 1 mL placebo × 1 syringe, 2 mL placebo × 2 syringes b. 1 mL active × 1 syringe, 2 mL active × 1 syringe, 1 mL placebo × 1 syringe, 2 mL placebo × 1 syringe c. 1 mL active × 2 syringes, 2 mL active × 2 syringes	1 mL placebo × 2 syringes 2 mL placebo × 2 syringes
Route of Administration	SC injection	SC injection
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Packaging and Labeling	Provided in glass container and labeled according to local requirement	Provided in glass container and labeled according to local requirement

Duration of Study Treatment and Participation

The duration of study participation for each subject is approximately 9 months, including ≤4 weeks of screening period, 4 weeks of placebo run-in period, 24 weeks of double-blind treatment period, and 4 weeks of final safety follow-up period.

6.2. Preparation/Handling/Storage/Accountability

PRV-015 will be supplied in a glass container and should be stored frozen at a temperature -30ºC (±10 ºC). Prolonged exposure to light should be avoided. The placebo solution should be stored refrigerated at 5 ± 3ºC.

An unblinded pharmacist at the site will prepare 4 syringes labeled for each subject. All syringes will be labeled with appropriate measures to maintain the blind.

Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to randomized study drug (placebo or 1 of 3 doses of PRV-015) after the single-blind, placebo run-in period using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Subjects will be randomly assigned in a 1:1:1:1 ratio, stratified by VH:CD of <2 or ≥2 (assessed during the placebo run-in period) and by the CeD PRO Abdominal Symptoms domain score of <3 or ≥3 at baseline, using the average of the Abdominal Symptoms domain scores over the last week of the run-in period immediately before randomization. The Investigator, Sponsor, and subjects will remain blinded to each subject's assigned study drug throughout the course of the study. In order to maintain this blind, an otherwise uninvolved pharmacist or equivalent staff member will be responsible for the reconstitution and dispensation of all study drug and will ensure that there are no differences in time taken to dispense following randomization.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study drug records at the site(s) to verify that randomization/dispensing has been done accurately.

Emergency Unblinding

The Investigator may unblind a subject through the IVRS/IWRS at any time for an emergency where the treatment assignment is important for the subject's medical care. However, if at all possible, it is recommended that the Investigator should consult with the Medical Monitor or Sponsor Medical Lead before unblinding. If the Investigator encounters difficulty in unblinding, the local clinical research associate can be reached for assistance.

6.4. Study Treatment Compliance

When subjects are dosed, they will receive the study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the case report form (CRF). The dose of study intervention and study subject identification will be confirmed at the time of study drug preparation by a member of the unblinded study site staff.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the subject is receiving at the time of screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Medications

The following medications are not allowed during the study (unless otherwise noted):

- Systemic or intestinal immune suppressants, including steroids. Inhaled or nasal steroids for respiratory diseases such as asthma and allergic rhinitis as well as topical steroids (except intestinal) are permitted.
- Oral pharmaceutical presentations (e.g., capsules) of probiotic supplements. Probiotics in foods (e.g., yogurt) are acceptable.
- Chronic or continuous oral and IV antibiotics (>2 weeks use). Topical antibiotic use is allowed.
- Systemic antiviral medications
- Systemic antifungal medications
- Live vaccines (within 14 days before Visit 3)
- Investigational drugs or devices

Note: After screening, use of any of these medications may be permitted if they are required for treatment of an AE, if the Investigator believes it is necessary. The use of any of these medications should be documented as a protocol deviation, even if they are used to treat AEs. The Investigator should inform the Medical Monitor of such use as early as possible.

6.6. Dose Modification

Subjects should receive the dose regimen as assigned through randomization. No dose modification during the double-blind treatment period is allowed. Patients who meet the criteria for study treatment discontinuation should follow the instructions in Section 7.1.

6.7. Treatment after the End of the Study

None.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Discontinuation of study treatment or withdrawal from the study will be noted in the subject's record.

7.1. Discontinuation of Study Treatment

In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study treatment. If a subject discontinues study drug administration after randomization (Visit 3), the subject will be encouraged to return for all subsequent on-site visits as listed in the SoA (i.e., Visits 4, 5, 7, 9, 11, 13, 14, 15, and 16). If the discontinued subject chooses to not return for on-site visits, study personnel should make every effort to conduct the Early Termination (ET) visit and ask the subject to return 6 weeks after the last dose of the study drug for the final safety follow-up visit (see Section 1.3). If a subject discontinues study drug administration before randomization, no further assessments will be conducted.

The reasons for permanent discontinuation of study treatment at any time during the study include but are not limited to the following:

- Safety reasons, either at the discretion of the Investigator or at the subject's request.
    - In particular, subjects can be discontinued from study treatment if they develop severe complications of celiac disease that require intensive treatment (e.g., RCD-I or RCD-II, jejunitis, perforation).
    - Malignancy
    - Active TB
    - A serious opportunistic infection
    - Pregnancy (female subjects)
    - Anaphylaxis or severe hypersensitivity reactions after the initial injection(s)
- Significant protocol violations (e.g., noncompliance with study procedures), at the discretion of the Sponsor
- The use of prohibited therapy that may interfere with the study assessment and analysis (Section 6.5.1). The Investigator is required to report all such information on the CRF and decide, upon discussion with the Sponsor, whether the subject is to be discontinued from study treatment.

7.1.1. Emergency Data Monitoring Committee Meeting

The DMC will hold an emergency meeting if any of the following occur:

- Death of a subject
- Anaphylactic reaction in any subject
- A life-threatening AE in any subject that is considered by the investigator to be possibly related to study drug

The DMC would review unblinded safety information to determine whether any change in study conduct should occur.

7.2. Subject Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request. If possible, the early termination assessments listed for Visit 15 (Week 24) in the SoA (Section 1.3) should be conducted before the withdrawal, including EGD with biopsy, unless the withdrawal occurs before randomization.

A subject who withdraws consent from the study will be permanently discontinued both from the study drug and from any further assessments.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not yet tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The site should attempt to contact the subject at least 3 times and document all such attempts before determining the subject has been lost to follow-up.

8. Study Assessments and Procedures

8.1. All Laboratory Tests

The maximum amount of blood collected from each subject over the duration of the study is expected not to exceed 400 mL over a period of approximately 9 months. This estimation does not include repeat or unscheduled samples, which may be taken for safety reasons or for technical issues with collected samples.

All laboratory tests to be conducted at in-office visits are listed as follows.

Screening Visit (within 28 days before Visit 1)

- Chemistry: calcium, ALT, AST, albumin, total and direct bilirubin, sodium, potassium, blood urea nitrogen (BUN), creatinine, chloride, CO_2, glucose, total protein, alkaline phosphatase (ALP) (if ALP is >3 x ULN, test 5'nucleotidase or GGT), magnesium, phosphorus
- Complete blood count (CBC): hemoglobin, hematocrit, platelets, white blood cell count (WBC) with differential, red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean cell hemoglobin (MCH)
- Urinalysis (dipstick and microscopic)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- HLA DQ2/8 (as needed)
- Testing for HIV, HBV and HCV for exclusion as follows:
  - HIV: positive antibody to p24 antigen (Ab-p24Ag) for human immunodeficiency virus (HIV) 1 or 2 confirmed by positive HIV 1/2 Western blot
  - HBV: HBsAg, anti-HBc total (IgM and IgG) confirmed by positive HBV DNA, anti-HBs
  - HCV: HCV antibody confirmed by positive HCV RNA
- IGRA
- *H. pylori* stool test
- Serum pregnancy test (all WOCBP only)
- FSH/LH for women with suspected menopause (i.e., not surgical menopause)
- Serum IgA
- Anti-tTG IgA and IgG, anti-DGP IgA and IgG

Visit 1 (Single-blind run-in Week -4)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy (WOCBP only)

Visit 2 (Single-blind run-in Week -2)

- Stool and urine gluten tests

- Urine pregnancy (WOCBP only)

Visit 3 (Week 0/Day 1)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Ferritin, iron, TIBC, vitamins D, B12, folate
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015
- ADA

Visit 4 (Week 2/Day 15)

- Stool and urine gluten tests
- Trough concentration of PRV-015
- ADA

Visit 5 (Week 4/Day 29)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015
- ADA

Visit 7 (Week 8/Day 57)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- Urinalysis (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015

Visit 9 (Week 12/Day 85)

- Chemistry (same tests as screening)

- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Ferritin, iron, TIBC, vitamins D, B12, folate
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015
- ADA

Visit 11 (Week 16/Day 113)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015

Visit 13 (Week 20/Day 141)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015

Visit 14 (Week 22/Day 155)

- Trough concentration of PRV-015
- ADA

Visit 15 (Week 24/Day 169) or Early Termination

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests

- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Ferritin, iron, TIBC, vitamins D, B12, folate
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015
- ADA

Visit 16 (Week 28/Day 197)

- Chemistry (same tests as screening)
- CBC (same tests as screening)
- HbA1C (subjects with diagnosed Type 1 or Type 2 diabetes only)
- Urinalysis (same tests as screening)
- Stool and urine gluten tests
- Urine pregnancy test (WOCBP only)
- Anti-tTG IgA, anti-DGP IgA
- Serum biomarkers (e.g., IL-15)
- Trough concentration of PRV-015
- ADA

8.2. Efficacy Assessments

8.2.1. Celiac Disease Patient-Reported Outcome (CeD PRO)

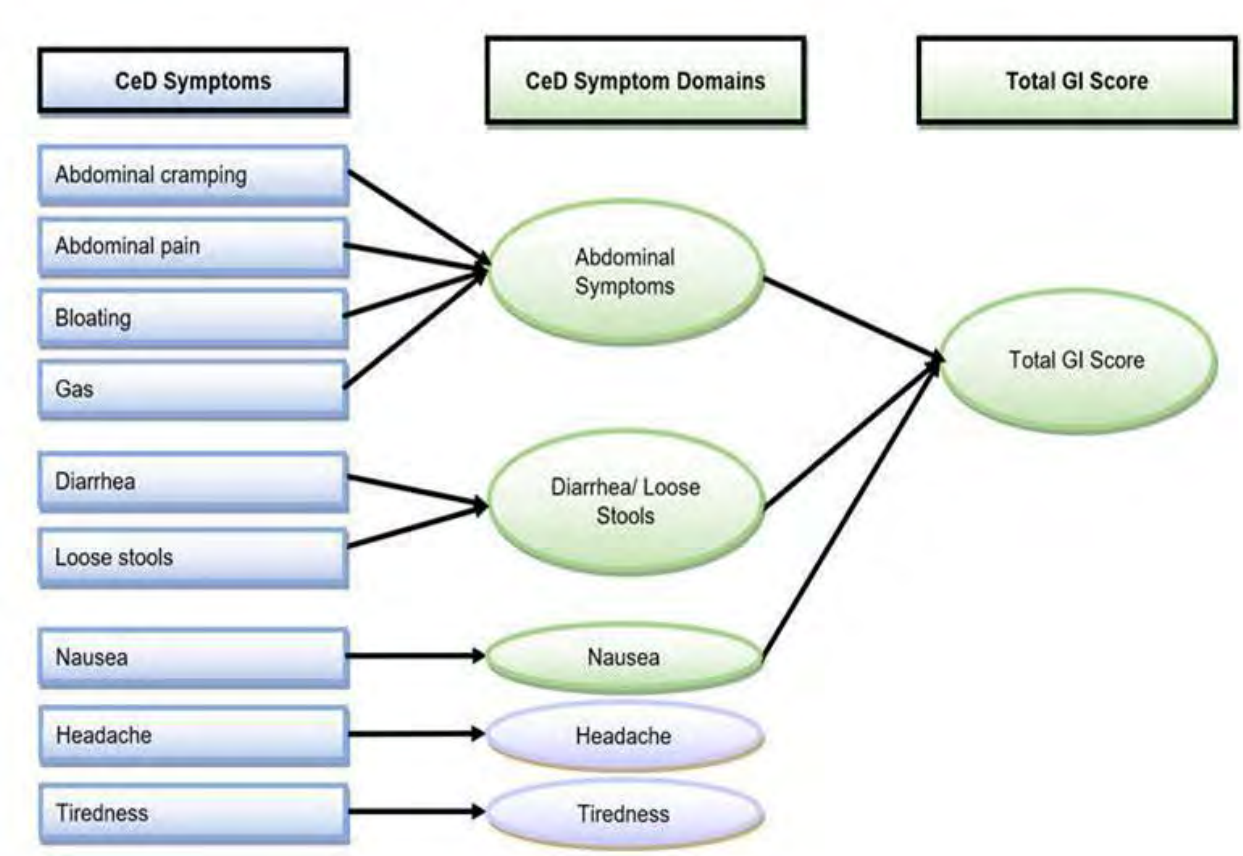
Subjects will assess their symptoms daily in the CeD PRO using the eDiary throughout the study. This questionnaire was specifically developed and validated to assess symptom severity in clinical trials of celiac disease (Leffler 2015) and is accepted by Health Authorities as a registrational endpoint for marketing authorization. The symptom domains within the CeD PRO are illustrated in Figure 2.

Items in the questionnaire were formulated based on one-on-one interviews with patients with celiac disease, thus they reflect the symptoms that patients consider part of their celiac disease experience. The questionnaire is designed as a self-administered daily diary to be completed at the same time each day and requires less than 10 minutes to complete. It includes 9 items asking participants about the severity of celiac disease symptoms they may experience each day. Participants are asked to rate their symptom severity on an 11-point (0 to 10) scale; from “not experiencing the symptom” to “the worst possible symptom experience”. Symptoms include abdominal cramping, abdominal pain, bloating, gas, diarrhea, loose stool, nausea, headache, and tiredness.

The Abdominal Symptoms domain refers to questions regarding abdominal pain, abdominal cramping, bloating, or gas in the CeD PRO questionnaire.

Analyses will be performed on all individual domain scores and weekly worst symptom domain scores in the GI domains (Abdominal Symptoms and Diarrhea/Loose Stool domains) and Total GI score (Abdominal Symptoms Domain + Diarrhea/Loose Stool Domain + Nausea item). The Total GI score will be assessed with and without inclusion of the Nausea item.

Figure 2 Symptom Domains in the Celiac Disease Patient-Reported Outcome Questionnaire



See Appendix 10.4 for the instrument.

8.2.2. Stool Frequency Question Based on BSFS

The BSFS is a pictorial aid to help subjects identify the shape and consistency of their stools during the study (Riegler 2001). The subject will be asked to record the number of stools that have a consistency of Type 6 or 7 (loose stool or entirely liquid) at bedtime daily in the eDiary. On the days in which the subject experiences no such stool (BSFS Type 6 or 7), the subject should record 0 in the eDiary instead of leaving it blank.

See Appendix 10.4 for the instrument.

8.2.3. Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a 15-question, 7-point-scale questionnaire used to assess 5 dimensions of GI syndromes: diarrhea, indigestion, constipation, abdominal pain, and reflux (Svedlund 1988). The recall period is 1 week before the assessment. While not specific for celiac disease, the GSRS is widely used in gastroenterology and has been used in several clinical trials of experimental medications in celiac disease (Kelly 2013; Lähdeaho 2011; Leffler 2015).

See Appendix 10.4 for the instrument.

8.2.4. Investigator Global Assessment of Disease

The IGA is a 5-point Likert scale designed for use by the Investigator or qualified sub-investigator to assess the subject's clinical disease activity at each specified time point. The same assessor should be used at each specified time point if possible.

See Appendix 10.4 for the instrument.

8.2.5. PROACTIVE Dietary Questionnaire

The PROACTIVE Dietary Questionnaire (See Appendix 10.4) is a two-question instrument to assess potential inadvertent exposure to gluten. The questionnaire will be completed on a weekly basis (every Monday) to assess dietary habits during the previous week.

8.2.6. Patient Global Impression of Severity and Change

In the current study, data collected from the PGIS and PGIC instruments will assist in future analyses of clinically meaningful change for the Abdominal Symptoms domain of the CeD PRO.

8.2.6.1. Patient Global Impression of Severity (PGIS)

Subjects will be asked to complete the PGIS every 2 weeks in the eDiary, from the evening of eDiary dispensation at Visit 1 (Day -28) through the end of the study.

Subjects will be asked to assess the severity of their symptoms as follows:

> "Please choose the response that best describes the severity of your celiac disease over the past 7 days (check one response): None, Mild, Moderate, Severe, Very Severe."

8.2.6.2. Patient Global Impression of Change (PGIC)

Subjects will be asked to complete the PGIC every 2 weeks in the eDiary, beginning 2 weeks after the first dose of study drug administration at Visit 1.

Subjects will be asked to compare their symptoms to those before treatment as follows:

> "Please choose the response below that best describes the overall change in your celiac disease symptoms since you started taking the study medication: Much better, A little better, No change, A little worse, Much worse."

8.2.7. Esophagogastroduodenoscopy (EGD) and Histological Assessments

At each time point specified in the SoA (Section 1.3), at a minimum, 6 biopsies or specimens of small-bowel tissue will be taken from the second part of the duodenum distal to the ampulla (duodenum D2) by EGD and endoscopic forceps biopsy. Ulcerative lesions should be avoided for all biopsies. The biopsies should be opaque and not translucent or stringy. Poor specimens should be replaced. The location and macroscopic appearance of the tissue will be noted in the source documents. The potential presence of any observable lesion such as ulcerative jejunitis will also be captured. When necessary, samples will be re-oriented and sectioned again until they are of good quality. The procedures will be described in a Study or Laboratory Manual or a similar document. The biopsies or specimens will be prioritized as follows:

1. All 6 specimens will be fixed in PAXgene at the site (see Central Laboratory Manual) and shipped to the Central Pathologist.
2. The Central Pathologist, blinded to treatment assignment, will assess villus height (VH, in micrometers) and crypt depth (CD, in micrometers) and their ratio, VH:CD, using 4 specimens. Further, the Marsh-Oberhuber histology score will be given (M0, M1, M2, M3a, M3b, or M3c) and the density of CD3-positive IELs (cells/100 epithelial cells) will be assessed. Histology analysis will be performed following standard operating procedures for fixed biopsy specimen orientation, paraffin embedding, cutting, staining, and scanning for whole slide virtual microscopy. Standard operating procedures will also be followed for biopsy morphometry readings using validated methods (Taavela 2013). If it is not feasible to measure at least 3 villus-crypt units for a subject's given biopsies, even after re-cutting, the results will be considered not evaluable.
3. Two specimens will be placed in a messenger ribonucleic acid (mRNA) preservative for future mRNA analysis of inflammatory pathways (e.g., expression analysis of IL-15-related pathways to potentially identify predictive biomarkers of response to PRV-015).

Every effort will be made to collect at least all 6 specimens, but if this number cannot be reached, the specimens will be allocated in the order indicated above. Sites may collect a maximum of 2 additional duodenal biopsy fragments for local clinical and/or research purposes. Additional biopsies of unexpected abnormalities or diseases that are excluded from the study may also be taken and processed locally.

8.2.8. Celiac Disease-Related Serology

Anti-tTG auto-antibodies, while not very responsive to modest dietary transgressions, constitute a specific tool to assess disease activity in response to large amounts of gluten over a period of time of at least 8-12 weeks (Lähdeaho 2011; Kelly 2013). Blood samples will be collected at the specified visits to determine the levels of serum anti-tTG antibodies (see Section 1.3). Anti-tTG IgA and IgG are analyzed in blood at screening and in serum thereafter using enzyme-linked immunosorbent assay (ELISA).

Anti-DGP antibodies are more responsive than anti-tTG to gluten consumption and have been detected in some celiac patients who are negative for anti-tTG due to the different kinetics between the antibodies and the possibility of IgA deficiency and a false negative anti-tTG IgA. Thus, anti-DGP IgG is a sensitive antibody to measure celiac disease activity (Brusca 2015). Blood samples will be collected to analyze serum anti-DGP antibodies (IgA) by ELISA at specified visits (see Section 1.3).

8.2.9. Gluten Stool and Urine Tests

The G12 antibody-based stool and urine gluten tests are validated assays used to assess patient compliance with gluten challenge and to measure possible gluten contamination in research studies. The assay detects and quantifies gluten consumption by measuring gluten immunogenic peptides in stool (Comino 2012) and urine (Moreno 2015).

Subjects are instructed to collect a stool sample approximately every 2 weeks, before each scheduled visit and bring it to the site or provide the sample during the visit if possible. If this is not possible, a stool sample collected within 3 days before and 3 days after a visit is acceptable.

For at-home visits, samples are not collected. Urine sample for gluten testing will be collected during the office visit.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

A complete physical examination, required at screening, Visit 1, Visit 15, and Visit 16, will include, at a minimum, assessments of the head, eyes, ears, nose and throat, cardiovascular, respiratory, gastrointestinal and neurologic systems and skin, extremities, and lymph nodes. A brief physical examination at other specified visits (Section 1.3) will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen), and areas of previously noted abnormalities.

Height will be measured and recorded at screening. Weight will be measured at all physical examinations.

8.3.2. Vital Signs

Vital signs include BP, respiratory rate, heart rate, and body temperature (axillary or oral).

Measurements of BP and heart rate will be assessed supine or sitting, after the subject has rested for at least 5 minutes in a quiet setting without distractions.

The investigator will note if vital signs are normal or abnormal and, if abnormal, whether they are clinically significant or not.

Cut-off values considered to be potentially clinically important (PCI) will be outlined in the Statistical Analysis Plan (SAP).

8.3.3. Electrocardiograms

Single 12-lead ECG will be obtained at screening for study eligibility. The Investigator should note whether it is normal, abnormal not clinically significant, or abnormal clinically significant.

8.3.4. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests are among the overall laboratory tests listed in Section 8.1.

The Investigator must review the laboratory report, document this review, and determine whether any clinically relevant changes occurring during the study should be classified as an AE or not.

Cut-off values for PCI laboratory abnormalities will be outlined in the SAP and Laboratory Manual.

8.4. Adverse Events and Serious Adverse Events

All AEs will be reported by the subject.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definitions of an AE or SAE (see Section 10.2) and remain

responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug (see Section 7).

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

All AEs and SAEs will be collected from the signing of the ICF through the final visit (Visit 16) as specified in the SoA (Section 1.3).

TEAEs will be collected from the first post-randomization dose of the study drug administration at Visit 3 through the final visit (Visit 16) as specified in the SoA (Section 1.3). The AEs and SAEs reported during the screening and single-blind placebo run-in periods will be reported separately from the TEAEs.

All SAEs will be recorded and reported to the sponsor or designee immediately upon observing or learning of the event and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.2. Information about the SAE should be as complete as possible and include causality. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.2.

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.4.7) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.2.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study drug under clinical investigation are met.

The Investigator is required to submit via email or facsimile the SAE form to the CRO, including a summary of relevant information, a diagnosis or symptom summary, and the Investigator's assessment of its relationship to study drug, within 24 hours. Follow-up information should be provided as it becomes available.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the study binder and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

All pregnancies in female subjects and female partners of male subjects that occur after randomization and the start of study drug administration will be collected through the final visit and up to 3 months after the last dose of the study drug, whichever is later.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.3.

The pregnancy should be followed until delivery or termination of the pregnancy. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6. Hospitalizations for Social Reasons or for Procedures

Hospitalization for social reasons or for procedures that do not generally require hospitalization such as for endoscopy, will not be considered as AEs.

8.4.7. Adverse Events of Special Interest

The treatment-emergent AESIs to be collected are severe opportunistic infections and hypersensitivity reactions of at least moderate severity.

8.5. Treatment of Overdose

Overdose (a dose above the highest dose specified in this protocol) is not expected in this study since the drug is administered by study personnel. No doses of PRV-015 above 600 mg or 8 mg/kg have been previously administered. The effects above these doses are unknown, and no antidote is available.

8.6. Pharmacokinetics and Immunogenicity

Blood samples will be collected at Visit 3 before the first post-randomization dose of study drug administration (baseline) and before the dose is given at each subsequent visit indicated in the SoA. Samples will be analyzed for serum trough concentration of PRV-015 (C_{min}) and ADA, as well as neutralizing antibodies (NAb), using validated assays.

Drug concentration information will not be reported to investigative sites or blinded personnel until the study is unblinded.

8.7. Pharmacodynamics and Biomarkers

Pharmacodynamic biomarkers to be explored in the study include, but are not limited to, the following parameters:

- Biomarkers of disease activity (such as serum IL-15)
- Anti-tTG IgA
- Anti-DGP IgA
- Other exploratory biomarkers

8.8. Genetics

Celiac genetic markers (typically HLA DQ2 and DQ8) will be assessed at screening for inclusion (Section 5.1), if the subject has not already been tested and the results available in the medical record. If a subject has previously obtained a test for HLA, the result will be recorded in the eCRF.

8.9. Quality of Life Measurements

The study personnel will evaluate subjects' quality of life using the ICDSQ questionnaire at study visits specified in the SoA (Section 1.3). The ICDSQ questionnaire (https://eprovide.mapi-trust.org/instruments/impact-of-celiac-disease-symptoms-questionnaire-c) is an instrument developed by Alvine Therapeutics to assess the impact of celiac disease symptoms on patients' quality of life (Acaster 2011).

In addition, EQ-5D-5L will be administered to subjects at the same visits as ICDSQ. The EQ-5D-5L is a 6-item, self-administered generic measure of health status and consists of two parts: a descriptive system and a visual analog scale (VAS). (https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf)

ICDSQ and EQ-5D-5L are included in Appendix 10.4.

9. Statistical Considerations

9.1. Statistical Hypotheses

The hypothesis of this study is that one or more dose groups of PRV-015 is effective in attenuating the symptoms of celiac disease compared with placebo in adult subjects with celiac disease who are symptomatic despite being on a GFD for at least 12 months.

9.2. Sample Size Determination

A proposed sample size of approximately 50 evaluable subjects within each treatment group would provide approximately 80% power to detect a 0.40 difference from placebo to any given active treatment group at the two-sided, 0.05 level of significance in the primary endpoint, change through Week 24 in the Abdominal Symptoms domain score in CeD PRO. These calculations are based on the assumption of a [redacted] within-subject standard deviation (SD), as derived in the CELIM-NRCD-001 trial using the mixed effect modeling for repeated measures (MMRM) analyses. An approximate [redacted] difference in the overall least squares (LS) means through 16 weeks in the treatment period was observed between the active (300 mg) and placebo groups. The overall estimate through 16 weeks was observed to be [redacted] for placebo versus [redacted] for the 300 mg treatment group. Of note, the estimated difference at week 16 was [redacted]; however, the more conservative overall difference of [redacted] was used in the calculation of sample size. The results and their ranking are exploratory in nature, and the selection of endpoints and dose for confirmatory studies will be based on the totality of evidence. As such, these calculations are not adjusted for multiplicity.

Approximately 220 subjects will be randomized at a ratio of 1:1:1:1 to PRV-015 100 mg, 300 mg, 600 mg, or placebo (approximately 55 subjects per group). Subjects will be stratified by normal or abnormal VH:CD (i.e., <2 or ≥2) and by the CeD PRO Abdominal Symptoms domain score of <3 or ≥3 at baseline using the average of the Abdominal Symptoms domain scores over the last week of the single-blind placebo run-in period immediately before randomization. The number of subjects with Marsh score of 0 or 1 will be capped at approximately 72. Withdrawn subjects will not be replaced.

9.3. Populations for Analyses

The following populations are defined as follows:

Population	Description
Intent to treat (ITT)	All randomized subjects. Subjects will be analyzed according to the treatment they are randomly assigned, regardless of the treatment they actually receive.

Population	Description
Per protocol (PP)	All subjects in the ITT population except those who have major protocol violations. Major protocol violations are defined as protocol deviations serious enough that are considered likely to affect the interpretation of the study results. These subjects will be identified prior to unblinding of the study and will be documented in the subject classification document. Subjects who withdraw due to lack of response or worsening of disease will be included in the PP analysis.
Safety	All randomized subjects who take at least 1 dose of the study drug post-randomization. Subjects will be analyzed according to the treatment they actually receive. In addition, safety results reported in the 4-week placebo run-in period will be reported separately from the active treatment period.

9.4. Statistical Analyses

The SAP will be finalized prior to unblinding and will include a detailed description of the statistical analyses, data derivation rules and handling of missing data.

Any differences between the protocol and the SAP will be documented in the SAP. Final statistical analyses will be based on the SAP.

9.4.1. General Considerations

All continuous endpoints and respective changes from baseline (absolute and percent) will be summarized (N, means, medians, SD, coefficients of variation [CV%], minimum and maximum). Rates or proportions will be tabulated by frequency of occurrence (count) and percent. All summaries will be by treatment and collection time.

Baseline values will be derived from observations collected in the placebo run-in period. For the CeD PRO Abdominal domain scores, baseline value will be the average of scores over the last week of the 4-week placebo run-in period immediately before randomization.

9.4.2. Primary Endpoint and Estimand

The primary endpoint is the change from baseline through Week 24 in the score of the Abdominal Symptoms domain of CeD PRO questionnaire, compared between the 3 PRV-015 dose groups and the placebo group.

The primary estimand is the difference in the overall mean values (averaged across 24 weeks) of each of the 3 PRV-015 treatment groups compared with placebo of the change from baseline in the Abdominal Symptoms domain of the CeD PRO questionnaire in the target population, regardless of compliance with study treatment or the occurrence of intercurrent events.

The primary endpoint will be tested for each of the 3 dose levels of PRV-015, 100 mg, 300 mg, or 600 mg against placebo, separately as follows:

H_{10}: $\mu_{PRV015\ (600mg)} = \mu_{Placebo}$

against the alternative

H_{11}: $\mu_{PRV015\ (600mg)} \neq \mu_{Placebo}$,

H_{20}: $\mu_{PRV015\ (300mg)} = \mu_{Placebo}$

against the alternative

H_{21}: $\mu_{PRV015\ (300mg)} \neq \mu_{Placebo}$, and

H_{30}: $\mu_{PRV015\ (100mg)} = \mu_{Placebo}$

against the alternative

H_{31}: $\mu_{PRV015\ (100mg)} \neq \mu_{Placebo}$

The primary efficacy endpoint will be summarized along with respective absolute and percent changes from baseline.

The primary efficacy endpoint (CeD PRO Abdominal Symptoms domain score) will be analyzed using linear mixed effect modeling for repeated measures (MMRM) with treatment, week, and week by treatment as fixed effects, the continuous baseline Abdominal Symptoms domain and VH:CD as covariates, and subject as a random effect.

Baseline Abdominal Symptoms domain score is defined as the average of the daily scores for the last week of assessment in the placebo run-in period. Baseline VH:CD is the measure from endoscopic biopsies performed during the placebo run-in period.

The base-model variance-covariance structure for the repeated measures data will be unstructured (UN). An autoregressive variance-covariance structure of order 1 [AR(1)] will be tested against the UN variance-covariance structure using likelihood ratio tests. An overall estimate of treatment effect as well as treatment differences will be provided along with the respective 95% confidence intervals (CIs). By-week estimates will be provided as well. All tests of statistical significance will be at two-sided, 0.05 level of significance. As the MMRM analysis assumes that data are missing at random, sensitivity analyses will be performed to assess affects from departure of this assumption.

The primary analyses will be conducted on the ITT population. Secondary analyses of the primary endpoint will be conducted on the PP population. Subgroup analyses of the primary endpoint will be conducted for each level of both stratification factors and for subjects showing at least 2 positive results from the stool or urine gluten tests post baseline, as well as those with 0 or 1 positive tests.

9.4.3. Secondary Endpoints

The secondary efficacy endpoints (Section 3) will be analyzed using the ITT and PP populations, as well as the subgroups described for the primary endpoint. This includes changes from baseline through Week 24 in the Diarrhea and Loose Stool Domain score and the Total GI score. Analyses will be performed on the IEL density (measured by IHC). The analyses will be comparable to the primary endpoint analysis and will be described in detail in the SAP.

9.4.4. Tertiary/Exploratory Endpoints

[redacted]

9.4.5. Safety Analyses

The Safety population will be used for all safety analyses. The safety variables, including AEs (coded using the Medical Dictionary for Regulatory Activities [MedDRA]) will be tabulated by actual treatment received. TEAEs, TEAEs leading to withdrawal, treatment-emergent SAEs, and AESIs will be tabulated by MedDRA system organ class and preferred term. PCI laboratory tests and vital signs will be tabulated and listed by visit. Additionally, AEs and SAEs will be tabulated separately for subjects enrolled in the 4-week placebo run-in period.

9.4.6. Pharmacokinetic and PK/PD Analyses

The geometric means and geometric CV% of PRV-015 minimum concentrations (C_{min}) will be reported by treatment group and time point in addition to N, mean, SD, min, and max. In

addition, dose proportionality, achievement of steady-state, and accumulation ratio based on C_{min} will be assessed. Associations of C_{min} with biomarkers of disease activity and other clinical endpoints may be explored. Dose proportionality will be analyzed using a power model, and potential PK/PD associations will mainly be assessed graphically and, if warranted, further elucidated with linear or nonlinear modeling techniques.

Additionally, absolute and changes from baseline in gluten-induced serum antibodies (anti-tTG and anti-DGP antibodies) will be listed and summarized by treatment group and collection visit. Relationships to dose and PK may be explored.

9.5. Interim Analysis

No formal interim analysis is planned for this study. An internal DMC will evaluate risk-benefit continually during the study and may recommend changes to study conduct.

Internal Data Monitoring Committee

An internal DMC will be set up to periodically evaluate trial-related data. The DMC will consist of at least 3 independent members not affiliated with the study. It will be chaired by a physician, and other members will include at least 1 physician and 1 statistician._The DMC will receive blinded and unblinded data before each meeting. The DMC will meet at least quarterly. The DMC may also hold emergency meetings in the event of death regardless of relatedness, life-threatening events possibly related to study drug, or anaphylaxis to advise on continued study conduct. Relevant medical literature may also be reviewed by the committee.

Complete guidelines, evaluation criteria, and other organizational and operational aspects will be documented in a DMC Charter.

An additional series of Safety Meetings will be held between the study team, including the Sponsor Safety Physician, and Amgen, the holder of the global safety database.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to local and other applicable regulatory requirements

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The Investigator or his/her designee will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign and date a statement of informed consent that meets local regulatory and/or IRB/IEC requirements.

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

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Investigator is responsible for ensuring that subject confidentiality is maintained for any documents submitted to the sponsor.

10.1.5. Committees Structure

A Safety Committee, consisting of the CRO Medical Monitor, Sponsor Medical Lead, Sponsor Safety Physician, and Pharmacovigilance Physician from the holder of the Global Safety Database, will be formed to provide oversight during the study. Other study team members may be included in the committee as well. Meetings with minutes will be held at least quarterly to assess the cumulative blinded safety tables and listings and to review relevant safety information of PRV-015 as it becomes available from other studies in other indications. Relevant medical literature may also be reviewed by the committee.

10.1.6. Dissemination of Clinical Study Data

The study information will be posted on www.ClinicalTrials.gov and EudraCT. The disclosure of study results will be compliant with regulatory requirements.

10.1.7. Data Quality Assurance

All relevant study data will be recorded, as appropriate, in the CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF at intervals determined by the Sponsor.

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

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.

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

The sponsor assumes accountability for actions delegated to other individuals (e.g., CRO).

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

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

Definition of what constitutes source data can be found in the study Monitoring Plan.

10.1.9. Study and Site Start and Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Sponsor may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to the Sponsor for review, according to the applicable Clinical Trial Agreement.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug. • A treatment-emergent AE (TEAE) is defined as an AE that occurs from the first dose of post-randomization study drug administration through the end of the study.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

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

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

10.2.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or within 3 months of the last dose, the Investigator will provide the Sponsor with a copy of the death certificate, hospitalization records and any post-mortem findings including histopathology where available • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting via Paper CRF
Within 24 hours of identifying an SAE, the Investigator must obtain an SAE Report Form, complete the form, and transmit it via email or FAX to the designated Pharmacovigilance contact. The SAE Report Form must contain all information required for CIOMS reporting. It should contain a check box for initial or follow-up reporting. Minimum information to be documented on the SAE report form: • Protocol number • Name and contact phone number of the Principal Investigator • Participant number and year of birth • SAE (preliminary diagnosis and SAE criterion), date of event onset, date of last study drug administration, brief narrative including current status of subject Investigator causality assessment MUST be provided • Concomitant medication information and treatments provided • Relevant laboratory/diagnostic test results and other relevant information Follow-up information should be provided with the same form with the Follow-up box checked.
SAE Reporting via eCRF
After transmitting the SAE report form, the eCRF should be completed for the SAE. This should be updated as the SAE is updated.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:

   - Surgical menopause is the result of removal of uterus with/without the ovaries
   - 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 may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female subjects and female partners with childbearing potential of male subjects must use a highly effective birth control method according to the Clinical Trials Facilitation and Coordination Group (CTFG) guidance.

Highly effective methods

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods, including:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Notes: Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

A man who is sexually active with a woman of childbearing potential and has not had a vasectomy or otherwise surgically sterile must agree to use highly effective birth control for their female partner and must use condoms with spermicide during sexual intercourse, and this must continue for 3 months after receiving the last dose of study drug. All men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated

delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy. A separate informed consent is required to collect the pregnancy-related information.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue study drug administration and be withdrawn from the study.

10.4. Appendix 4: Assessment Instruments

10.4.1. Celiac Disease Patient-Reported Outcome Questionnaire

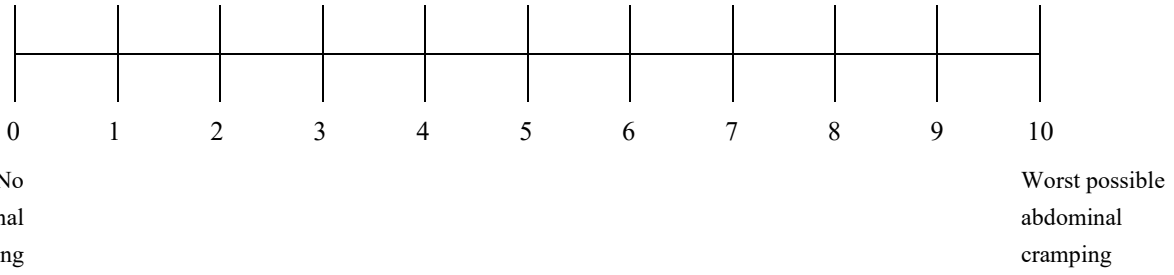
An electronic version of the CeD PRO will be administered in PRV-015-002b. Instructions, items, and response scales of the CeD PRO are presented in this Appendix.

Celiac Disease Patient-Reported Outcome Questionnaire

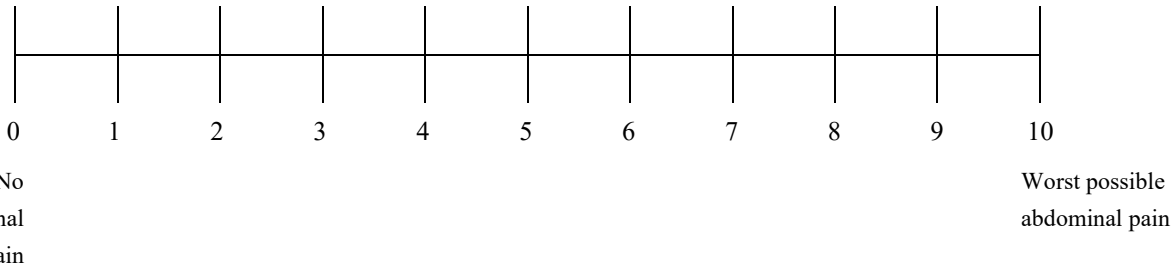
Instructions: These questions ask about how you feel each day. Please complete the daily diary every evening, at approximately the same time.

1. **Thinking about your worst experience in the past 24 hours, how severe was each of the following symptoms? On the following screens, please tap a number to indicate how you felt.**

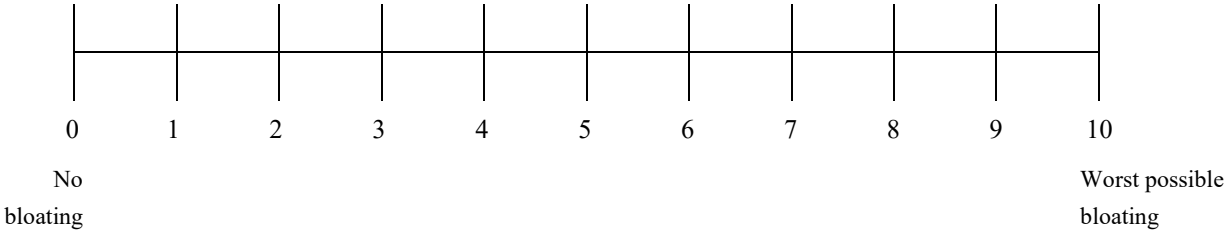
   a. How severe was your abdominal cramping?



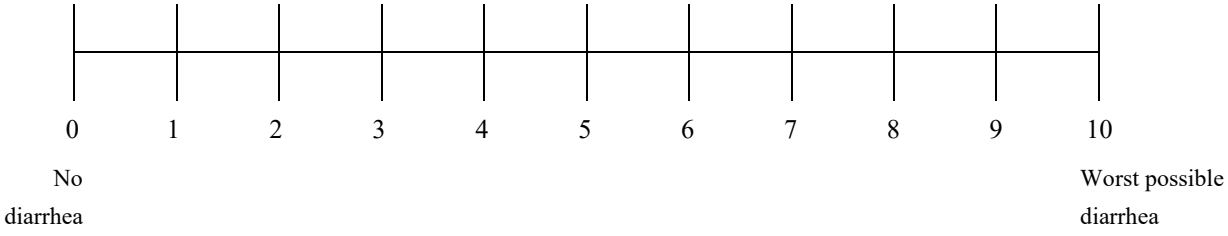
   b. How severe was your abdominal pain?



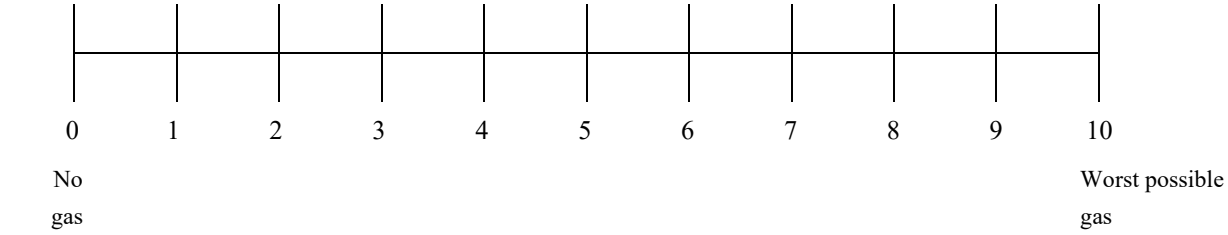
c. How severe was your bloating?



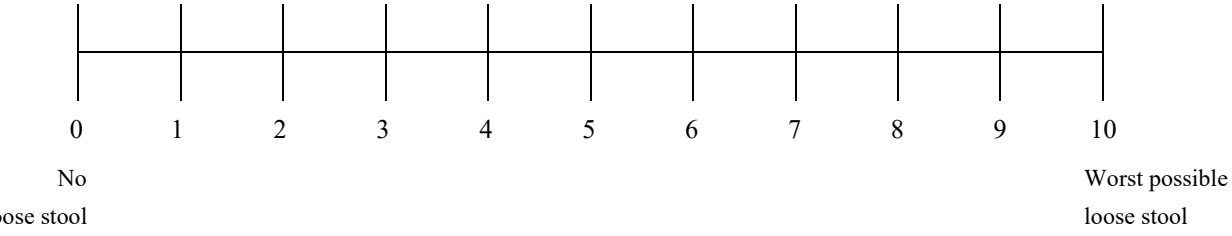
d. How severe was your diarrhea?



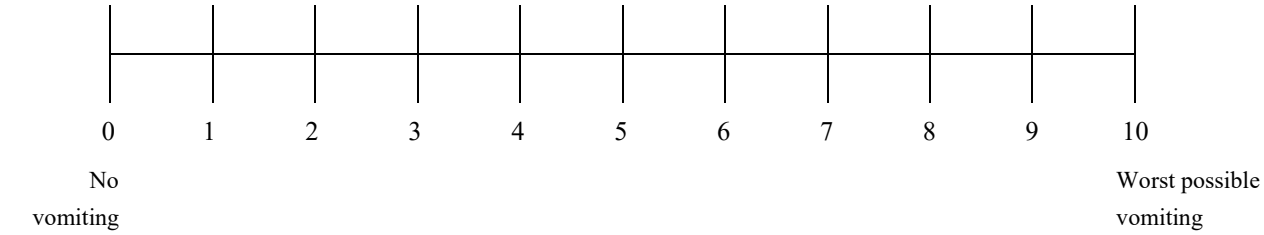
e. How severe was your gas (flatulence)?



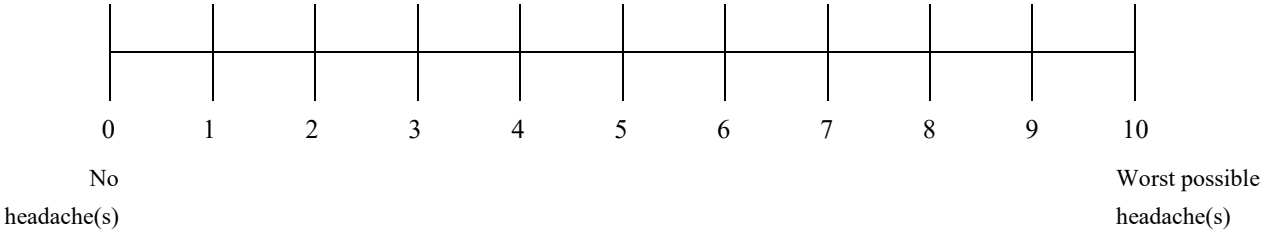
f. How severe was your loose stool?



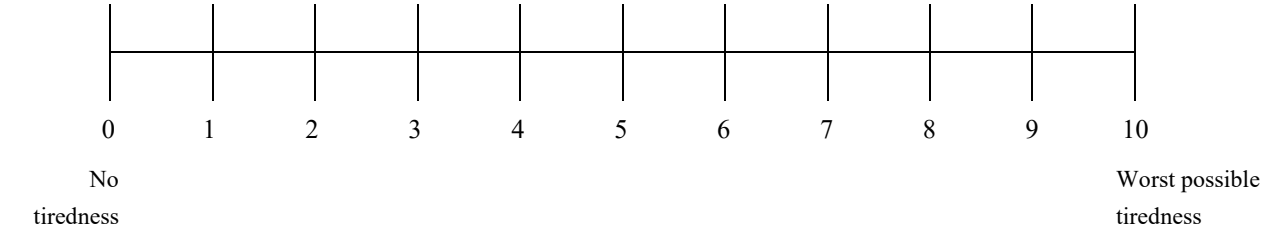
g. How severe was your nausea?



h. How severe was your headache(s)?



i. How severe was your tiredness?



10.4.2. Gastrointestinal Symptom Rating Scale

THE GASTROINTESTINAL SYMPTOM RATING SCALE (GSRS)

Please read this first:

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

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

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

2. Have you been bothered by HEARTBURN during the past week? (By heartburn we mean an unpleasant stinging or burning sensation in the chest.)

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

3. Have you been bothered by ACID REFLUX during the past week? (By acid reflux we mean the sensation of regurgitating small quantities of acid or flow of sour or bitter fluid from the stomach up to the throat.)

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

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

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

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

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

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

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

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

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

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

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

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

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

10. Have you been bothered by CONSTIPATION during the past week? (Constipation refers to a reduced ability to empty the bowels.)

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

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

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

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

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

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

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

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

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

15. When going to the toilet during the past week, have you had the SENSATION OF NOT COMPLETELY EMPTYING THE BOWELS? (This feeling of incomplete emptying means that you still feel a need to pass more stool despite having exerted yourself to do so.)

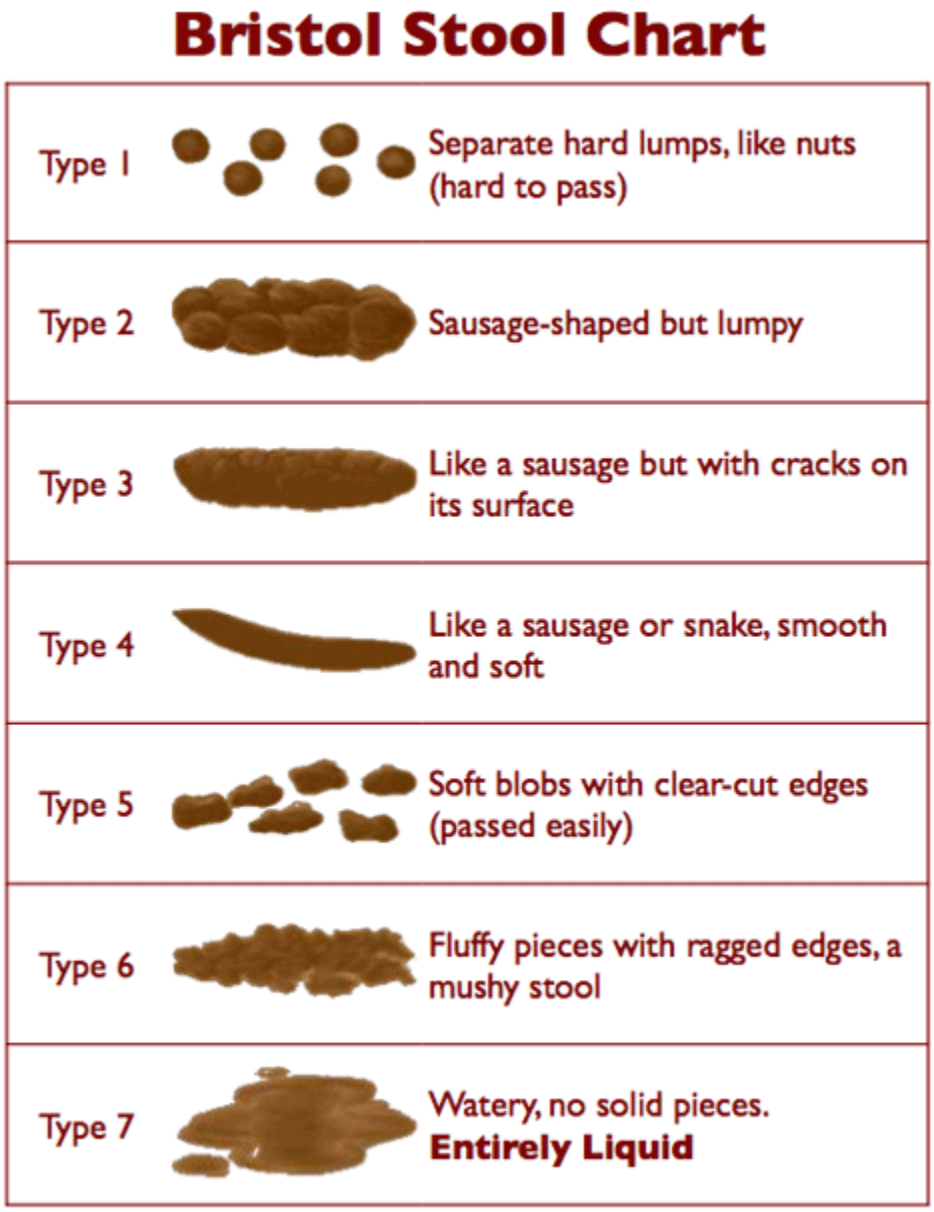
- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!

THANK YOU FOR YOUR CO-OPERATION.

10.4.3. Stool Frequency Question

In the past 24 hours, how many stools did you have that had a consistency that are Type 6 or 7 on the chart (Bristol Stool Form Scale) below?



10.4.4. Investigator Global Assessment (IGA)

Based on the information available, choose the box that best represents the subject's current overall disease activity:

□ Inactive Disease

□ Mild Disease

□ Moderate Disease

□ Severe Disease

□ Very Severe Disease

10.4.5. Patient Global Impression of Severity (PGIS)

Please choose the response that best describes the severity of your celiac disease over the past 7 days (check one response):

- None
- Mild
- Moderate
- Severe
- Very Severe

10.4.6. Patient Global Impression of Change (PGIC)

Please choose the response below that best describes the overall change in your celiac disease symptoms since you started taking the study medication:

- Much better
- A little better
- No change
- A little worse
- Much worse

10.4.7. PROACTIVE Dietary Questionnaire

The following questions ask about your dietary activities as they relate to your celiac disease during the past 7 days.

During the past 7 days:

1. How many days did you consume a meal prepared outside of your home?

- ◉ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7

2. How many days do you think you consumed gluten?

- ◉ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7

10.4.8. Impact of Celiac Disease Symptoms Questionnaire (ICDSQ)

Impact of Coeliac Disease Symptoms Questionnaire© (ICDSQ©)

To what extent have your coeliac disease symptoms (e.g. diarrhoea, constipation, bloating) affected you over the ***past 7 days?***

Please respond to each question by marking an "X" in the box to indicate your response.

DAILY ACTIVITIES	**Not at all**	**A little**	**Moderately**	**Very Much**	**Completely**
Over the past 7 days…					
1. My day-to-day life has been disrupted by my coeliac disease symptoms	☐	☐	☐	☐	☐
2. My coeliac disease symptoms have disrupted my sleep	☐	☐	☐	☐	☐
3. My coeliac disease symptoms have interfered with my work (including housework, paid and unpaid work, home maintenance and studying)	☐	☐	☐	☐	☐
4. I have been less effective with my work (including housework, paid and unpaid work, home maintenance and studying) because of my coeliac disease symptoms	☐	☐	☐	☐	☐
SOCIAL ACTIVITIES	**Not at all**	**A little**	**Moderately**	**Very Much**	**Completely**
Over the past 7 days…					
5. My coeliac disease symptoms have negatively affected my social activities	☐	☐	☐	☐	☐
6. My coeliac disease symptoms have interfered with my enjoyment of social events	☐	☐	☐	☐	☐
7. My coeliac disease symptoms negatively affected my daily interactions with my family or friends	☐	☐	☐	☐	☐

Version 03Nov2011

ICDSQ – United Kingdom/English – Original version
ICDSQ_AU1.0_eng-GBori

EMOTIONAL WELLBEING		Not at all	A little	Moderately	Very Much	Completely
	Over the past 7 days…					
8.	I felt embarrassed because of my coeliac disease symptoms	☐	☐	☐	☐	☐
9.	I felt anxious because of my coeliac disease symptoms	☐	☐	☐	☐	☐
10.	I felt angry because of my coeliac disease symptoms	☐	☐	☐	☐	☐
11.	I felt annoyed because of my coeliac disease symptoms	☐	☐	☐	☐	☐
12.	I felt sad because of my coeliac disease symptoms	☐	☐	☐	☐	☐
PHYSICAL ACTIVITIES		**Not at all**	**A little**	**Moderately**	**Very Much**	**Completely**
	Over the past 7 days…					
13.	My coeliac disease symptoms have interfered with my participation in physical activities (exercise, sport, walking etc)	☐	☐	☐	☐	☐
14.	My coeliac disease symptoms have interfered with my enjoyment of physical activities (exercise, sport, walking etc)	☐	☐	☐	☐	☐

Please check back through the questions one more time and make sure you are happy with your answer.

Make sure you thought about ***the last 7 days*** and the impact of **your coeliac disease symptoms.**

THANK YOU

10.4.9. EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

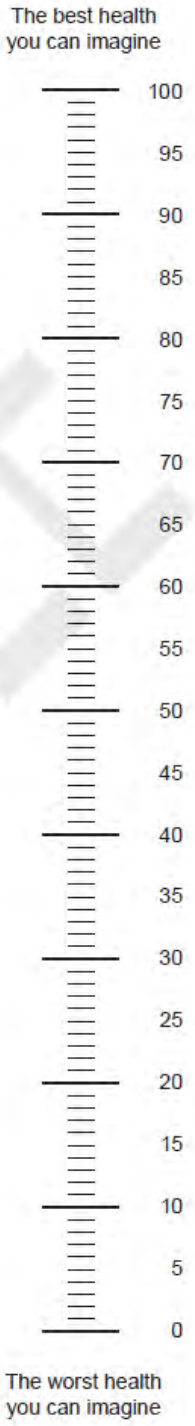
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



10.5. Appendix 5: Interpretation of Hepatitis Results

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total (IgM and IgG)):

1. Subjects who test negative for all HBV screening tests (i.e., HBsAg-, anti-HBc-, and anti-HBs) are eligible for this study.
2. Subjects who test positive for HBsAg are not eligible for this study, regardless of the results of other hepatitis B tests.
3. Subjects who test negative for HBsAg and test negative for anti-HBc and positive for anti-HBs are eligible for this study.
4. Subjects who test positive for anti-HBc and anti-HBs are not eligible for this study unless HBV DNA test is negative. If the HBV DNA test cannot be performed, the subject is not eligible.
5. Subjects who test positive for anti-HBc must undergo further HBV DNA test. If the HBV DNA test is positive, the subject is not eligible for this study. If the HBV DNA test is negative, the subject is eligible. In the event the HBV DNA test cannot be performed, the subject is not eligible.

	Hepatitis B test result		
Eligibility Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Exclude	+	− *or* +	− *or* +
Include	−	−	−
	−	+	−
Require HBV DNA testing*	−	− or +	+

* If HBV DNA is detectable, exclude from the trial. If HBV DNA testing cannot be performed, exclude from the trial.

10.6. Appendix 6: Abbreviations

Abbreviation or Specialist Term	Explanation
ACG	American College of Gastroenterology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
BSFS	Bristol Stool Form Scale
BUN	blood urea nitrogen
CBC	complete blood count
CeD PRO	Celiac Disease Patient-Reported Outcome
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{min}	trough concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CV%	coefficient of variation
DGP	deamidated gluten peptide
DMC	Data Monitoring Committee
EATL	enteropathy-associated T-cell lymphoma
ECG	electrocardiogram
eDiary	electronic diary
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
ET	early termination
FSH	follicle-stimulating hormone

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GFD	gluten-free diet
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
HbA1c	hemoglobin A1c
HEENT	head, eyes, ears, nose, throat
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICDSQ	Impact of Celiac Disease Symptoms Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IEL	intraepithelial lymphocytes
Ig	immunoglobulin
IGA	Investigator Global Assessment
IGRA	Interferon Gamma Release Assay
IHC	immunohistochemistry
IL	interleukin
IL-15Rα	interleukin 15 receptor alpha unit
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LH	luteinizing hormone
mAb	monoclonal antibody
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration

Abbreviation or Specialist Term	Explanation
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect modeling for repeated measures
mRNA	messenger ribonucleic acid
NAb	neutralizing antibody
NRCD	non-responsive celiac disease
PCI	potentially clinically important
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PP	per protocol
q2w	every 2 weeks
QoL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell count
RCD-II	refractory celiac disease Type II
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SoA	schedule of activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse events
TNFα	tumor necrosis factor alpha
tTG	tissue transglutaminase
ULN	upper limit of normal
VH:CD	villous height-to-crypt depth ratio
WBC	white blood cell count
WOCBP	women of childbearing potential

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