NCT Number: NCT04424927

STATISTICAL ANALYSIS PLAN

Study 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
Study No/Code	PRV-015-002b (PROACTIVE)
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This study is conducted in accordance with GCP

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALL	All screened analysis set
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ATC	Anatomic Therapeutic Classification
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AR(1)	first order auto-regressive
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BLQ	below the limit of quantitation
BMI	body mass index
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
CMH	Cochran–Mantel–Haenszel test
C_{min}	trough concentration
Css	average steady state trough concentration
CRF	case report form
CRO	contract research organization
CV%	coefficient of variation

DGP	deamidated gliadin peptide
DMC	Data Monitoring Committee
ECG	electrocardiogram
eDiary	electronic diary
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCV	Geometric Coefficient of Variation
GFD	gluten-free diet
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GIP	Gluten Immunogenic Peptides
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
IMG	Immunogenicity
IRB	Institutional Review Board
IRT	Item Response Theory
ITT	intent to treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LH	luteinizing hormone
LLQ	Lower Limit of Quantitation
LS	least -squares
mAb	monoclonal antibody
MAR	missing at random
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	modified Intent to Treat analysis set
MMRM	mixed effect model for repeated measures
MNAR	missing not at random
mRNA	messenger ribonucleic acid
NAb	neutralizing antibody

NCMV	neighboring-case missing values
nMiss	number of missing observations
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
PT	Preferred Term
q2w	every 2 weeks
QoL	quality of life
RA	rheumatoid arthritis
Rac	accumulation ratio
RBC	red blood cell count
RCD-II	refractory celiac disease Type II
RIS	Run-in analysis set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SC	subcutaneous(ly)
SD	standard deviation
SMQ	Standardized MedDRA query
SoA	schedule of activities
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse events

TIBC	Total iron binding capacity
TNFα	tumor necrosis factor alpha
tss	Time at which 90% of the subject specific Css is achieved
tTG	tissue transglutaminase
ULN	upper limit of normal
UN	unstructured
ULQ	Upper limit of quantitation
VAS	Visual analog scale
VH:CD	villous height-to-crypt depth ratio
WBC	white blood cell count
WOCBP	women of childbearing potential

2 INTRODUCTION

This is a statistical analysis plan (SAP) for study PRV-015-002b which is based on the study protocol v3.0 (dated 24MAR2022). This SAP describes the statistical analyses which will be presented in the clinical study report.

The SAP is a supplement to the study protocol, which should be referred to for additional details on study objective, endpoints, study design, study conduct, and other operational aspects of the study.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective, Endpoint and Estimand

The **primary objective** is:

- To assess the efficacy of PRV-015 in attenuating the symptoms of celiac disease in adult patients with Non-Responsive Celiac Disease (NRCD) as measured by the Abdominal Symptoms domain of the Celiac Disease Patient-Reported Outcome (CeD PRO) questionnaire.

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 in the change from baseline in the Abdominal Symptoms domain of the CeD PRO questionnaire in the mITT population, regardless of compliance to study treatment or the occurrence of intercurrent events.

3.2 Secondary Objectives and Endpoints

The **secondary objectives** are:

- 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.

The **secondary efficacy endpoints** are:

- 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).

The **secondary safety endpoints** are:

- 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.

The **secondary PK endpoint** is:

- Serum PRV-015 trough concentrations (C_{min}).

3.3 Other Objectives and Endpoints

The **tertiary/exploratory objectives** are:

[redacted]

The **tertiary/exploratory endpoints** are:

[redacted]

4 STUDY TYPE AND DESIGN

This 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 gluten-free diet (GFD).

After signing the 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 x 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 Bristol Stool Form Scale [BSFS]). 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 baseline 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. A minimum of four daily recordings are required for derivation of the weekly mean Abdominal Symptoms domain score. Enrollment of subjects with Marsh score 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) (Appendix 11.1). Clinical assessments occur from Visit 3 through Visit 16 of the double-blind randomized treatment period. 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.

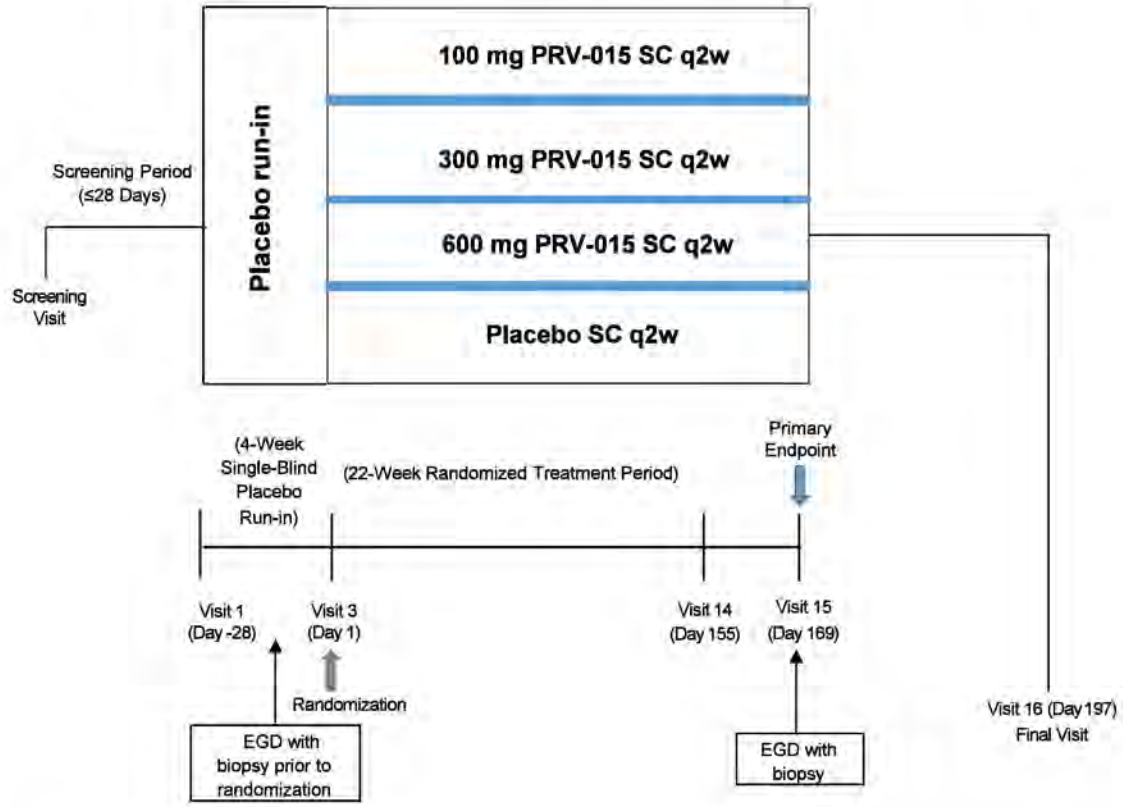
Visits 6, 8, 10, and 12 may be conducted either at the site or remotely by certified mobile personnel per the Investigator's decision.

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).

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

Figure 1. Study Schema



5 RANDOMIZATION

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 baseline 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.

6 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.

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 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}: $\mu_{PRV\text{-}015\ (600mg)} = \mu_{Placebo}$

against the alternative

H_{11}: $\mu_{PRV\text{-}015\ (600mg)} \neq \mu_{Placebo}$,

H_{20}: $\mu_{PRV\text{-}015\ (300mg)} = \mu_{Placebo}$

against the alternative

H_{21}: $\mu_{PRV\text{-}015\ (300mg)} \neq \mu_{Placebo}$, and

H_{30}: $\mu_{PRV\text{-}015\ (100mg)} = \mu_{Placebo}$

against the alternative

H_{31}: $\mu_{PRV\text{-}015\ (100mg)} \neq \mu_{Placebo}$

where $\mu_{PRV\text{-}015\ (600mg)}$, $\mu_{PRV\text{-}015\ (300mg)}$, $\mu_{PRV\text{-}015\ (100mg)}$ and $\mu_{Placebo}$ denote the mean change from baseline through Week 24 of Abdominal Symptoms domain score in the high dose, medium dose, low dose and placebo arm, respectively. Each of the three hypotheses will be tested using a two-sided, 0.05 level of significance with no adjustment for multiple comparisons.

7 ESTIMATION OF SAMPLE SIZE

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 and 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 modelling 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 baseline 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 0 or 1 will be capped at approximately 72. Withdrawn subjects will not be replaced.

8 STATISTICAL METHODS

8.1 Analysis Sets

8.1.1 All screened (ALL) analysis set

The ALL analysis set consists of all screened subjects.

8.1.2 Run-in (RIS) analysis set

The RIS analysis set includes subjects who take at least 1 dose of the single-blind placebo during the run-in period.

8.1.3 Intent-to-Treat (ITT) analysis set

The ITT analysis set includes all randomized subjects. Subjects will be analyzed according to the randomized treatment.

8.1.4 Modified Intent-to-Treat (mITT) analysis set

The mITT analysis set includes all randomized subjects who received at least one dose of double-blind treatment. Subjects will be analyzed according to the randomized treatment.

8.1.5 Per-protocol (PP) analysis set

The PP analysis set includes all mITT subjects 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 deviations may include, but are not limited to:

- Randomization of a patient that does not meet inclusion or exclusion criteria
- Study medication administered shorter than the protocol-specified window
- Took prohibited medications during the study as defined in the protocol
- Treatment compliance <80% during the double-blind period

These subjects will be identified prior to unblinding of the study and will be documented in the subject classification document. Subjects who do not have a major protocol violation but withdraw due to lack of response or worsening of disease will be included in the PP analysis set.

8.1.6 Pharmacokinetics (PK) analysis set

The PK analysis set includes subjects who are randomized, dosed, and have at least 1 post-dose evaluable PK assessment.

8.1.7 Immunogenicity (IMG) analysis set

The Immunogenicity analysis set includes subjects who are randomized, dosed, and have at least 1 evaluable immunogenicity assessment.

8.1.8 Safety analysis set

The safety analysis set includes all subjects who take at least 1 dose of the study drug post-randomization. Subjects will be analyzed according to the treatment they actually received. Any subject randomized to placebo who incorrectly receives one or more doses of PRV-015 will be analyzed as receiving PRV-015 and any subject randomized to PRV-015 who incorrectly only receives placebo doses will be analyzed as receiving placebo. If any subject received multiple PRV-015 dose levels, subject will be analyzed at the highest dose received.

Overview of the different analysis sets, and their usage is presented in Table 1. Data listings will primarily present all randomized subjects' data (i.e. based on ITT population)

Table 1. Overview of the Different Analysis Sets and Their Usage

	ALL	RIS	ITT	mITT	PP*	PK	IMG	Safety
Disposition	X							
Demographics and baseline characteristics			X	X	X			
Primary efficacy endpoint, primary analysis				X	X			
Primary efficacy endpoint, sensitivity analyses				X				
Primary efficacy endpoint, subgroup analyses				X				
Secondary efficacy endpoints				X	X			
Secondary efficacy endpoints, subgroup analyses				X				
Other efficacy endpoints				X				
Secondary safety endpoints (single-blind placebo run-in period)		X						
Secondary safety endpoints (post-randomization period)								X
Secondary Pharmacokinetics Endpoints						X		
Secondary Immunogenicity Endpoints							X	

* Additional analysis on PP analysis set may be added where deemed necessary.

8.2 General Statistical Considerations

Single-blind placebo run-in period is defined as a period for 4 weeks, starting at visit 1.

Treatment emergent period is defined from the first dose of double-blind study drug at visit 3 until the last dose of double-blind study drug + 42 days (i.e., to the end of 4-week safety follow-up period).

Post-treatment period is defined from the end of treatment emergent period.

All outputs are summarized by treatment and visit, if applicable.

Outputs will generally use the following header structure (label and order):

Placebo	PRV-015 100 mg	PRV-015 300 mg	PRV-015 600 mg
N = xx	N = xx	N = xx	N = xx

Total of PRV-015 groups is added for safety and baseline outputs or where relevant in the following way:

Placebo	PRV-015 100 mg	PRV-015 300 mg	PRV-015 600 mg	Total PRV-015
N = xx	N = xx	N = xx	N = xx	N = xx

All statistical tests will be two-sided at the 0.05 level of significance without multiplicity adjustment. In addition to the inferential statistics, 95% confidence intervals will be constructed.

Various covariates will be included in the models and will be retained in the respective models regardless of their significance or lack thereof. The list of variables to be included is described in detail in the following sections.

SAS codes provided in the appendix 11.4 may be modified based on statistical considerations, without requiring SAP amendment.

8.2.1 Descriptive Statistics

For continuous variables, the following descriptive statistics will be provided, unless stated otherwise: number of non-missing observations (n), number of missing observations (nMiss), mean, median, standard deviation (SD), minimum, maximum, Q1 and Q3 quartiles. Additional statistics will be provided for PK-related data, including the geometric mean ($mean_{geo}$) and geometric CV% ($CV\%_{geo}$).

For categorical variables, number of non-missing observations and frequency with percentage per category will be displayed. Denominators for percentages are the number of subjects with non-missing values in the pertinent analysis set and treatment group as appropriate, unless otherwise specified.

The number of missing observations (nMiss) is displayed only if > 0. For continuous variables it is displayed after the number of non-missing observations, for categorical variables it is displayed last in category.

8.2.2 Definition of Derived Variables

8.2.2.1 Patient-reported Assessments Captured in eDiary

CeD PRO Domain Scores

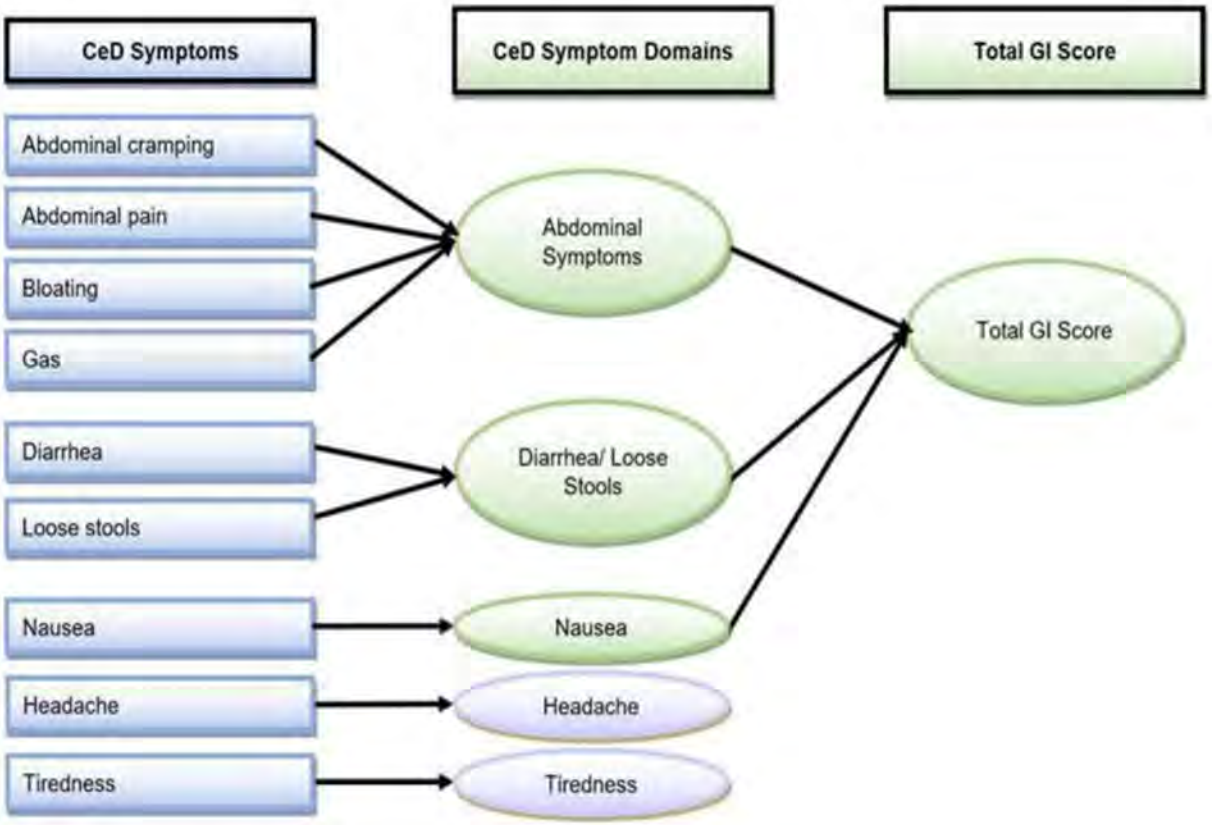
The CeD PRO is captured daily in the eDiary after the last meal of the day before the subject goes to bed. It includes 9 items asking participants about the severity of celiac disease symptoms they may experience each day. Participants are asked to rate their symptom severity on an 11-point (0 to 10) 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 (Figure 2).

Analyses will be performed on all individual domain scores and weekly worst symptom domain scores in the GI symptom 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.

Daily mean domain score is calculated as sum of daily item scores for all items within a domain divided by number of items in the domain.

Weekly domain scores are based on analysis visit windows (defined below) and calculated as the sum of non-missing daily mean domain scores divided by the number of non-missing scores of a given week. A weekly score is calculated if there are at least 4 non-missing daily scores available. Weekly mean total GI score is calculated as the sum of weekly mean Abdominal Symptoms domain score, Diarrhea and Loose Stools domain score, and Nausea item score divided by 3. The weekly mean total GI domain score without the Nausea item, is calculated as the sum of weekly mean Abdominal Symptoms domain score, Diarrhea and Loose Stools domain score divided by 2. If any of the weekly domains are missing, the total score will be calculated as the average over the remainder non-missing weekly domain scores.

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



CeD PRO Symptomatic Days

Symptomatic days will be assessed in terms of the Abdominal Domain, Diarrhea and Loose Stool Domain, and Total GI score of the CeD PRO. A given day is defined as a symptomatic day if any of the domain scores is >0. A day is considered asymptomatic if all of these scores are 0. The number of symptomatic days and asymptomatic days will be derived by month (including baseline) [based on month-based visit windows defined below] and total during the double-blind treatment period (through Week 24).

Weekly Worst Symptom Domain Score in CeD PRO

Weekly worst symptom domain scores will be derived separately for each of the following three domains: 1) Abdominal Domain score, 2) Diarrhea and Loose Stool Domain score, and 3) Total GI score by selecting the worst daily score for all items within each domain for a given week (based on analysis visit windows defined below) and averaging these scores.

BSFS Stools of Type 6 or 7

The BSFS is a pictorial aid to help subjects identify the shape and consistency of their stools during the study (Riegler et al, 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. The sum of weekly stool frequency (sum of the previous 7 days) through Week 24 for stools of BSFS Type 6 or 7 will be calculated, based on the analysis visit windows (defined below). In case of multiple records for stool in one day the latest record in time will be considered.

Baseline Value for Patient-Reported Assessments captured in eDiary

In general, the last non-missing value prior to the first dose of double-blind treatment will be used as the baseline value.

For patient-reported assessments captured in the eDiary, the following definitions of baseline in Table 2 will be used:

Table 2. Definition of Baseline for Patient-Reported Assessments Captured in eDiary

Assessment	Baseline Definition
CeD PRO (Abdominal domain and other weekly domain scores)	Average of scores from 7 days prior to randomization (e.g., last week of placebo run-in).
BSFS	Sum of Type 6 or 7 stool experienced over the 7 days prior to the date of first dose of double-blind treatment.
PGIC/PGIS	Most recent assessment prior to the first administration of double-blind treatment.
PROACTIVE Dietary Questionnaire	Most recent assessment prior to the first administration of double-blind treatment.

Visit Windowing (post-baseline) for Patient-Reported Assessments captured in eDiary

Analysis visit windows will be applied for following patient-reported eDiary assessments for post-baseline visits and are described below:

- CeD PRO
- BSFS
- PGIS/PGIC
- Weekly Diet Questionnaire

CeD PRO analysis visit windows (for week-based analysis).

In case of missing visit, the prior visit + 14 days will be taken.

Period	Analysis Visit	Days included in analysis window
Double-blind treatment	Week 2	Days -7 to -1 prior to actual Visit 4 date
Double-blind treatment	Week 4	Days -7 to -1 prior to actual Visit 5 date
Double-blind treatment	Week 6	Days -7 to -1 prior to actual Visit 6 date
Double-blind treatment	Week 8	Days -7 to -1 prior to actual Visit 7 date
Double-blind treatment	Week 10	Days -7 to -1 prior to actual Visit 8 date
Double-blind treatment	Week 12	Days -7 to -1 prior to actual Visit 9 date
Double-blind treatment	Week 14	Days -7 to -1 prior to actual Visit 10 date
Double-blind treatment	Week 16	Days -7 to -1 prior to actual Visit 11 date
Double-blind treatment	Week 18	Days -7 to -1 prior to actual Visit 12 date
Double-blind treatment	Week 20	Days -7 to -1 prior to actual Visit 13 date
Double-blind treatment	Week 22	Days -7 to -1 prior to actual Visit 14 date
Double-blind treatment	Week 24	Days -7 to -1 prior to actual Visit 15 date

CeD PRO analysis visit windows (for month-based analysis of symptomatic days)

Period	Month	Days included in analysis window
Run-in	Baseline	Days -28 to -1 prior to Actual Visit 3 date
Double-blind treatment	1	Actual Visit 3 date (inclusive) through day prior to actual Visit 5 date if available, or Visit 3 date + 28 days (if Visit 5 is missing)
Double-blind treatment	2	Actual Visit 5 date (inclusive) through day prior to actual Visit 7 date if available, or Visit 5 date + 28 days (if Visit 7 is missing) or Visit 7 – 28 days if Visit 5 is missing
Double-blind treatment	3	Actual Visit 7 date (inclusive) through day prior to actual Visit 9 date if available, or Visit 7 date + 28 days (if Visit 9 is missing) or Visit 9 – 28 days if Visit 7 is missing
Double-blind treatment	4	Actual Visit 9 date (inclusive) through day prior to actual Visit 11 date if available, or Visit 9 date + 28 days (if Visit 11 is missing) or Visit 11 -28 days if Visit 9 is missing
Double-blind treatment	5	Actual Visit 11 date (inclusive) through day prior to actual Visit 13 date if available, or Visit 11 date + 28 days (if Visit 13 is missing) or Visit 13 – 28 days if Visit 11 is missing
Double-blind treatment	6	Actual Visit 13 date (inclusive) through day prior to actual Visit 15 date if available, or Visit 13 date + 28

		days (if Visit 15 is missing) or Visit 15 – 28 days if Visit 13 is missing

BSFS analysis visit windows

In case of missing visit, the prior visit + 14 days will be taken.

Period	Analysis Visit	Days included in analysis window
Double-blind treatment	Week 2	Days -7 to -1 prior to actual Visit 4 date
Double-blind treatment	Week 4	Days -7 to -1 prior to actual Visit 5 date
Double-blind treatment	Week 6	Days -7 to -1 prior to actual Visit 6 date
Double-blind treatment	Week 8	Days -7 to -1 prior to actual Visit 7 date
Double-blind treatment	Week 10	Days -7 to -1 prior to actual Visit 8 date
Double-blind treatment	Week 12	Days -7 to -1 prior to actual Visit 9 date
Double-blind treatment	Week 14	Days -7 to -1 prior to actual Visit 10 date
Double-blind treatment	Week 16	Days -7 to -1 prior to actual Visit 11 date
Double-blind treatment	Week 18	Days -7 to -1 prior to actual Visit 12 date
Double-blind treatment	Week 20	Days -7 to -1 prior to actual Visit 13 date
Double-blind treatment	Week 22	Days -7 to -1 prior to actual Visit 14 date
Double-blind treatment	Week 24	Days -7 to -1 prior to actual Visit 15 date

PGIS/PGIC analysis visit windows

In general, PGIS/PGIC assessments closest to the target date will be selected; if there are equidistant assessments on either side of the actual visit date, the assessment prior to the visit date will be used.

Period	Analysis Visit	Target Visit Date
Double-blind treatment	Week 2	Closest to actual Visit 4 date
Double-blind treatment	Week 4	Closest to actual Visit 5 date
Double-blind treatment	Week 6	Closest to actual Visit 6 date
Double-blind treatment	Week 8	Closest to actual Visit 7 date
Double-blind treatment	Week 10	Closest to actual Visit 8 date
Double-blind treatment	Week 12	Closest to actual Visit 9 date
Double-blind treatment	Week 14	Closest to actual Visit 10 date
Double-blind treatment	Week 16	Closest to actual Visit 11 date
Double-blind treatment	Week 18	Closest to actual Visit 12 date
Double-blind treatment	Week 20	Closest to actual Visit 13 date
Double-blind treatment	Week 22	Closest to actual Visit 14 date
Double-blind treatment	Week 24	Closest to actual Visit 15 date

PROACTIVE dietary questionnaire analysis visit windows

In general, PROACTIVE dietary questionnaire assessments closest to the target date will be selected; if there are equidistant assessments on either side of the actual visit date, the assessment prior to the visit date will be used.

Period	Analysis Visit	Target Visit Date
Double-blind treatment	Week 2	Closest to actual Visit 4 date
Double-blind treatment	Week 4	Closest to actual Visit 5 date
Double-blind treatment	Week 6	Closest to actual Visit 6 date
Double-blind treatment	Week 8	Closest to actual Visit 7 date
Double-blind treatment	Week 10	Closest to actual Visit 8 date
Double-blind treatment	Week 12	Closest to actual Visit 9 date
Double-blind treatment	Week 14	Closest to actual Visit 10 date
Double-blind treatment	Week 16	Closest to actual Visit 11 date
Double-blind treatment	Week 18	Closest to actual Visit 12 date
Double-blind treatment	Week 20	Closest to actual Visit 13 date
Double-blind treatment	Week 22	Closest to actual Visit 14 date
Double-blind treatment	Week 24	Closest to actual Visit 15 date

8.2.2.2 Visit windowing for other assessments

Visit windowing for months will be applied to gluten tests to determine an absence or presence of gluten. Refer to the SAP section on the primary estimand and handling of intercurrent events.

No analysis windows will be applied to Anti-TTG antibody IgA, Anti-DGP antibody IgA, IL-15 biomarkers, or safety assessments. By-visit analyses will be presented using the nominal time points.

8.2.2.3 Change from Baseline

Absolute change from baseline is defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase compared to baseline.

Percent change from baseline is defined as

[(post-baseline value – baseline value) / (baseline value)] x 100.

8.2.3 Imputing Missing Values

Primary Endpoint

Imputation of missing values for sensitivity analysis of the primary endpoint is described in detail in Section 8.6.1.3.

BSFS Stools of Type 6 or 7

Weekly scores are calculated by summing the previous 7 days. Missing days within a given week will be imputed as the average of the non-missing days for a given assessment week for the derivation

of weekly sums. Weekly score is calculated if there are at least 4 non-missing daily scores available. If there are less than 4 non-missing daily scores, weekly score will be counted as missing.

Laboratory Assessments

For all clinical laboratory assessments, values below the lower limit of quantitation (LLQ) will be assigned a value of 0.5 x LLQ for summary statistics and values over the upper limit of quantitation (ULQ) will be assigned a value of ULQ for summary statistics.

PK Concentrations

PRV-015 concentrations below the LLQ will be assigned a value of 0.5 x LLQ in mean calculations for the summary of PRV-015 concentrations.

Missing and Partial Dates

Missing dates for Adverse Events and Concomitant Medications

For completely missing AE or CM start dates, the following applies:

- If end date is missing or it is after the start of the DB treatment date, then the start of the DB treatment date is used.
- If end date is in the SB placebo run-in phase, the start date of the event is imputed as the start of the SB placebo run-in date.
- If end date is in the screening phase, the start date of the event is imputed as the start of the screening date.

For completely missing end dates, the event is considered to be ongoing. No imputation will be done on completely missing end dates.

Partial dates for Adverse Events and Concomitant Medications

For partial start and end dates, the minimum possible date is imputed for start date and maximum possible date is imputed for end date. For example, if partial start date is "SEP2020" and partial end date is "OCT2020" then the imputed start date is "01SEP2020" and the imputed end date is "31OCT2020".

As a conservative approach, if day was imputed for the start date and the start of the DB study treatment date has the same month, then the DB study treatment start date is used instead. For example, if partial date is "SEP2020" and the 1st dose of the DB study treatment was administered on 05SEP2020, then the partial start date is also imputed as "05SEP2020". Similarly, in case when a partial start date has both day and month imputed but the year equals the year of the 1st dose of DB study treatment date, then the partial start date is imputed as the DB study treatment start date. For example, if partial date is "2020" and DB study treatment was administered on 05SEP2020, then the partial start date is imputed as "05SEP2020".

Partial dates for Celiac Disease Diagnosis Date

For date of diagnosis of celiac disease, if both month and day are missing, they will be imputed as mid-year (i.e., July 1st). If only day is missing, the day will be imputed as the 15th of the month.

Missing date for Investigator Global Assessment

Missing dates for the Investigator Global Assessment (IGA) in the eCRF will be assumed to be the same date as other assessments captured in the eCRF for the same nominal visit.

8.2.4 Handling of Data from Discontinued Subjects

Generally, the data from subjects who discontinue the study will be presented up to the point of discontinuation. Subjects who discontinue the study prior to randomization will not be included in ITT, mITT, PP or safety analysis set. Subjects who permanently discontinue the treatment will be included in the analysis set(s) based on the analysis set inclusion definition.

A subject who permanently discontinues treatment will be encouraged to return for all subsequent on-site visits as listed in the SoA (Appendix 11.1), 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, the Early Termination (ET) visit should be done and subject is asked to return 6 weeks after the last dose of the study drug for the final safety follow-up visit.

If subject decides to permanently discontinue the study, the early termination assessments listed for Visit 15 (Week 24) should be conducted before the withdrawal, including EGD and biopsy, unless the withdrawal occurs before randomization.

8.3 Disposition of Subjects, Analysis sets, and Major Protocol Deviations

Disposition of subjects includes the following tabulations of subjects by treatment, where appropriate:

- Screened
- Screen failures
    - Failed initial screening
    - Re-screened and failed re-screening
- Entered single-blind placebo run-in phase, not dosed
- Treated with single-blind placebo in run-in phase
- Failed during the run-in phase
- Discontinued during the run-in phase, including reason
- Randomization failures
- Randomized
- Randomized, not dosed
- Treated with double-blind treatment
- Discontinued the double-blind treatment, including reason
- Discontinued the study, including reason
- Completed the study

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.
Run-in failures are defined as those who enter the single-blind placebo run-in phase but do not continue past Visit 2 of the 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 at Visit 3 and therefore are not randomized to a treatment group.

The number and percentage of subjects in each analysis set will be summarized by treatment group. Disposition will also be summarized by country and site.

Major protocol deviations will be summarized by treatment group for the ITT analysis set.

Disposition of subjects, inclusion/exclusion criteria not met, informed consent dates, randomization information, protocol deviations and run-in, treatment, and study discontinuations will also be listed by subject.

Disposition is done on the ALL analysis set.

8.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics include:

- Age (years) at initial screening
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Stratification factor from IRT system: VH:CD of <2 or ≥2
- Stratification factor from IRT system: CeD PRO Abdominal Symptoms domain score of <3 or ≥3
- GSRS at screening
- Time since celiac disease diagnosis (months), calculated as (Date of randomization - Date of celiac disease diagnosis)/30.4375
- Anti-tTG Antibodies IgG
- Anti-DGP Antibodies IgG

Demographics and baseline characteristics are assessed at screening or prior to randomization (stratification variables). Demographic and baseline characteristics will be listed and summarized by treatment group. Demographics and baseline characteristics are presented on mITT, ITT, and PP (if applicable) analysis set. Efficacy and safety baseline characteristics not presented here are presented in the respective efficacy and safety tables.

Demographic information, baseline characteristics, and other information (e.g., HLA-DQ at Screening) will be provided in data listings.

8.5 Prior and concomitant medications and medical history

Prior and concomitant medications will be collected throughout the study. Medications will be coded using the latest WHO Drug dictionary available at the time of the database lock.

Prior medications are those which start and stop prior to the start of double-blind treatment. Concomitant medications are those which continue into the double-blind treatment period or begin after the start of double-blind treatment. Any medication that cannot be confirmed as stopping before the start date of the double-blind period will be classified as a concomitant medication.

Concomitant medications will be summarized by ATC 1, preferred name, and treatment group. All prior and concomitant medications will be listed for the ITT analysis set.

Medical history will be coded using the latest Medical Dictionary of Regulatory Activities (MedDRA) available at the time of the database lock. Medical history will be collected during screening and summarized by dose and overall total by system organ class and preferred term, on the mITT analysis set. Summaries will be ordered by descending order of the overall incidence of system organ class and preferred term within each system organ class.

Medical history conditions, will be presented on a by-subject listing, using the ITT analysis set.

Treatment Compliance

Treatment compliance (%) will be estimated and presented for the double-blind treatment period in the mITT analysis set. Compliance for a subject will be performed as [total number injections received]/[total planned number of injections]*100.

Total number injections received = Number of injections summed from the Study Drug Administration eCRF page over Visits 3 through Visit 14

Total planned number of injections = (Number of planned visits in double-blind period from Visit 3 through the earlier of Visit 14 and Study Discontinuation)*4

Summary statistics of treatment compliance will be provided by treatment group. The number and percentage of subjects in each category of treatment compliance (<80%, 80-<100%, 100%, >100%) will be presented by treatment group.

Treatment compliance will also be provided in a data listing for mITT analysis set.

8.6 Analysis of Efficacy

8.6.1 Primary Efficacy Variable(s)

The primary efficacy variable is the change from baseline through Week 24 in the score of the Abdominal Symptoms domain of CeD PRO questionnaire.

8.6.1.1 Primary Estimand and Handling of Intercurrent Events

The primary estimand corresponding to the primary efficacy variable consists of the following attributes:

A. Target Population

Adult patients with non-responsive celiac disease who have attempted a gluten free diet for at least 12 months as defined by the inclusion and exclusion criteria in the study protocol.

B. Endpoint

Absolute change from baseline through Week 24 in abdominal symptoms as measured by the Abdominal Symptoms domain of the CeD PRO questionnaire.

C. Population-Level Summary

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.

D. Strategy for Addressing Intercurrent Events

Treatment policy strategy, i.e. all collected primary endpoint data is used regardless of intercurrent events.

Intercurrent events are events which occur after treatment initiation and may interfere with the analysis of the primary endpoint. Intercurrent events are considered to be the following:

- Intake of prohibited medications
- Presence of gluten

As per treatment policy strategy intercurrent events are handled by collecting all primary endpoint data following any intercurrent event.

Intercurrent event counts and timings will be summarized by treatment group. Additional analysis may be done to further explore the effect of intercurrent events.

Intake of Prohibited Medication

The number of subjects who have taken at least one prohibited medication after randomization will be tabulated by treatment group.

The time (in weeks) from randomization to the first instance of a prohibited medication will also be summarized by treatment group. This time will be calculated as (start date of first post-randomization prohibited medication – randomization date + 1)/7.

The following medications are considered prohibited medications, even if they were used to treat AEs, as indicated in the study protocol:

- 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 Study Visit 3)
- Investigational drugs

If such medication was prescribed as needed ("prn") or was taken after Visit 16, it will not be considered as an intercurrent event.

The full list of subjects who have taken a prohibited medication will be identified in a blinded manner prior to database lock and study unblinding.

Absence or Presence of Gluten

Subjects are categorized into Absence or Presence of gluten category based upon having negative stool and urine gluten tests or having positive test result for either stool or urine gluten test, respectively. If both tests are missing or one test is missing and the other one is negative the visit will be missing. If one test is positive and the other one is missing it will be presence. This will be assessed using the nominal visit for urine or stool gluten samples. Positive stool gluten test is defined as the values above 0.156 µg GIP/g. Positive urine gluten test result is defined as the values above 6.25 ng GIP/ml. Number of subjects with absence or presence of gluten will be tabulated by treatment group. Each subject could be counted in both absence and presence category at different visits.

Month	Month ending visit	Qualifying Absence	Qualifying Presence
0	Visit 3	Stool and Urine gluten both negative at Visit 3	Stool or Urine gluten positive at Visit 3
1	Visit 5	Stool and Urine gluten both negative at Visit 5	Stool or Urine gluten positive at Visit 5
2	Visit 7	Stool and Urine gluten both negative at Visit 7	Stool or Urine gluten positive at Visit 7
3	Visit 9	Stool and Urine gluten both	Stool or Urine gluten positive at Visit 9

		negative at Visit 9	
4	Visit 11	Stool and Urine gluten both negative at Visit 11	Stool or Urine gluten positive at Visit 11
5	Visit 13	Stool and Urine gluten both negative at Visit 13	Stool or Urine gluten positive at Visit 13
6	Visit 15	Stool and Urine gluten both negative at Visit 15	Stool or Urine gluten positive at Visit 15

Time (in weeks) from first dose to the first time observing the presence of gluten will also be captured for each subject. This will be calculated as (Visit date corresponding to the first presence of gluten– date of first dose of double-blind treatment + 1)/7.

Subjects having an absence or presence of gluten will be presented in a data listing.

8.6.1.2 Primary Model

The primary efficacy variable will be analyzed using linear mixed effect modelling for repeated measures (MMRM) assuming data missing at random (MAR) with treatment, week, and week by treatment as fixed effects, the continuous baseline Abdominal Symptoms domain score and VH:CD ratio 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 the placebo run-in period. Baseline VH:CD is the measure from endoscopic biopsies performed during the placebo run-in period.

The variance-covariance structure to be used is unstructured (UN). If model convergence is not achieved, a first-order auto-regressive structure [AR(1)] will be considered. Additional variance-covariance structure might be explored in case of non-converge issue.

An overall estimate of treatment effect as well as treatment differences for the active treatment groups (600 mg, 300 mg, 150 mg) compared to placebo will be provided along with the respective 95% confidence intervals (CIs). By-week estimates and 95% CI will be provided as well. All tests of statistical significance will be at two-sided, 0.05 level of significance.

The following model will be fitted:

$$Y_{ijk} = \mu + \alpha_j + \gamma_k + \lambda_{jk} + \beta_1 \cdot baseline\ Abdominal\ Symptoms\ score_{ij} + \beta_2 \cdot baseline\ VH{:}CD\ ratio_{ij} + \eta_i + \varepsilon_{ijk}$$

where

Y_{ijk} is the change from baseline of Abdominal Symptoms weekly domain score for subject i $(i = 1, \ldots, n_j)$ from treatment group j $(j = 1, 2, 3, 4)$ at week k $(k = 2,4, \ldots, 24)$,

μ is the overall mean change from baseline,

α_j is the fixed effect due to treatment j,

γ_k is the fixed effect due to week k,

λ_{jk} is the fixed interaction effect due to treatment j and week k,

β_1 is the parameter estimate for the baseline Abdominal Symptoms score,

β_2 is the parameter estimate for the baseline VH:CD ratio,

η_i is the random effect due to subject i,

ε_{ijk} is the random error term for subject i from treatment group j at week k.

The observed baseline and post-baseline values along with the change from baseline values (absolute and percent) will also be summarized by treatment group and week (Weeks 2, 4, ..., 24). Baseline and post baseline values for the weekly scores will also be listed.

Mean (±SD) line plots by treatment group will be presented for both absolute values and changes from baseline for the observed data.

The primary analysis will be conducted on mITT analysis set and repeated on the PP analysis set.

8.6.1.3 Sensitivity Analyses for Primary Model to evaluate missing data imputation methods

The primary model is a linear mixed model assuming data missing at random (MAR). Sensitivity analyses are done to assess the robustness of the primary efficacy analysis results with respect to different methods of handling missing values, under missing not at random (MNAR) assumption.

For the analysis of the primary efficacy endpoint, missing data will be imputed at the week level using Multiple Imputation (MI) after applying the visit windowing strategy for the CeD PRO weekly scores.

The MI will be carried out following 3 steps:

Step 1. Generation of imputed datasets

The PROC MI procedure of the SAS system with MCMC statement will first be used impute intermittent missingness by treatment group in order to generate 100 sets of data with monotone missingness. Subsequently, PROC MI will be used with MNAR statement indicating the neighboring-case missing values (NCMV) method (Molenberghs and Kenward, 2007) in order to impute the monotone missing values to obtain complete data sets. The imputation model will include treatment group, continuous baseline CeD PRO Abdominal Symptoms domain score, VH:CD at baseline, and CeD PRO Abdominal Symptoms weekly domain score at previous time points as covariates.

Step 2. Model-based analysis using each imputed dataset

Each of the 100 imputed datasets will be analyzed using the primary model specified in Section 8.6.1.2.

Step 3. Pooling the results from each model-based analysis

The results from the analysis of each imputed dataset will be combined using Rubin's rule (Rubin, 1987) by implementing the PROC MIANALYZE procedure of the SAS system.

8.6.1.4 Sensitivity Analyses of Primary Model to Evaluate Effect of Intercurrent Events

If evaluation of intercurrent events (Section 8.6.1.1) indicates need for analysis of the primary endpoint in the presence of intercurrent events, the primary analysis will be repeated separately in the mITT analysis set addressing each of the following adjustments, after visit windowing is applied for the CeD PRO weekly data:

Prohibited Medication: Data collected prior to first use of prohibited medication will be used as observed. Time points after first use of prohibited medication will first be set to missing. The MI procedure in Section 8.6.1.3 will then be applied.

Presence of Gluten:

For subjects who do not experience presence of gluten per Section 8.6.1.1, all observed data will be used.

For subjects who experience the first presence of gluten, data from the visits prior to the presence of gluten will be used as observed. Once the first presence of gluten is experienced, observed data is only used from later visits if they meet the definition of absence of gluten. Visits exhibiting the presence of gluten will be set to missing and follow a similar multiple imputation procedure as in 8.6.1.3, with the exception that missing data will be imputed using data at those visits from placebo subjects who did not experience a presence of gluten.

Example 1 – Subject does not meet definition of presence – all observed data used

	Visit 3	Visit 5	Visit 7	Visit 9	Visit 11	Visit 13	Visit 15
Gluten Tests	Negative/ Negative	Negative/ Negative	Negative / Negative	Negative / Negative	Negative / Negative	Negative/ Negative	Negative/ Negative
Data used	Observed	Observed	Observed	Observed	Observed	Observed	Observed

Example 2 – Subject meets definition of presence at Visit 7 – imputation using placebo at visit 7

	Visit 3	Visit 5	Visit 7	Visit 9	Visit 11	Visit 13	Visit 15
Gluten Intake Tests	Negative/ Negative	Negative/ Negative	Positive/ Positive	Positive/ Negative	Negative/ Positive	Negative/ Negative	Negative/ Negative
Data used	Observed	Observed	Presence Impute Visit 7	Presence Impute Visit 9	Presence Impute Visit 11	Observed	Observed

8.6.1.5 Sensitivity Analysis of Primary Model to Evaluate Alternate Baseline Definition

In some instances, randomized patients who needed to be rescheduled for their Visit 3 (e.g., first dose of double-blind treatment) experienced delays between the end of their run-in period and the first dose of double-blind treatment. In this regard, a sensitivity analysis will be conducted for the primary model (Section 8.6.1.2) in the mITT analysis set to use the following baseline definition for the CeD PRO Abdominal symptoms domain:

- Average of scores from 7 days prior to the first dose of double-blind treatment.

In some instances, subjects were not compliant with completing the CED PRO questionnaire daily in the week prior to randomization. In this regard, a sensitivity analysis will be conducted for the primary model (Section 8.6.1.2) in the mITT analysis set to use the following baseline definition for the CeD PRO Abdominal symptoms domain:

- Alternative baseline will be defined as the 'Average of scores from 10 days prior to randomization (e.g., last 10 days of placebo run-in)'.

8.6.1.6 Subgroup Analyses of Primary Model

Subgroup analyses will be conducted in the mITT analysis set to explore the consistency of treatment effects in the following subgroups:

- VH:CD ratio (<2, >=2)
- Baseline CeD PRO Abdominal Symptoms domain score (<3, >=3)

[redacted]

[redacted]

For each subgroup, models similar to the primary model will be fit separately for each level of the subgroup.

8.6.2 Secondary Efficacy Variable(s)

Secondary efficacy variables of the study are:

- 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).

8.6.2.1 CeD PRO Diarrhea and Loose Stool Domain

The same type of model as for the primary endpoint will be fitted to the secondary CeD PRO endpoint for the change from baseline in Diarrhea and Loose Stool domain; i.e. including treatment, week, and week by treatment as fixed effects, the continuous baseline Abdominal Symptoms domain score and VH:CD ratio as covariates, and subject as a random effect.

These analyses will be done on the mITT analysis set and repeated on the PP analysis set.

8.6.2.2 Total GI Score

The same type of model as for the primary endpoint will be fitted to the secondary CeD PRO endpoint for the change from baseline in Total GI score (comprising the Abdominal Symptoms domain, the Diarrhea and Loose stool domain, and the Nausea item); i.e. including treatment, week, and week by treatment as fixed effects, the continuous baseline Abdominal Symptoms domain score and VH:CD ratio as covariates, and subject as a random effect.

These analyses will be repeated for the Total GI Score (excluding Nausea).

These analyses will be done on the mITT analysis set and repeated on the PP analysis set.

8.6.2.3 IEL Density

The absolute change from baseline to Week 24 in small intestinal mucosal inflammation, as measured by IEL density (cells/100 epithelial cells) using IHC will be analyzed using analysis of covariance (ANCOVA), where the continuous baseline Abdominal Symptoms domain score and VH:CD ratio are included as covariates and treatment as fixed effect.

The following model will be fitted:

$$Y_{ij} = \mu + \alpha_j + \beta_1 \cdot baseline\ Abdominal\ Symptoms\ score_{ij} + \beta_2 \cdot baseline\ VH{:}CD\ ratio_{ij} + \varepsilon_{ij},$$

where

Y_{ij} is the change from baseline to week 24 in small intestinal mucosal inflammation for subject i ($i = 1, \ldots, n_j$) from treatment group j ($j = 1, 2, 3, 4$),

μ is the overall mean change from baseline,

α_j is the fixed effect due to treatment j,

β_1 is the parameter estimate for the baseline Abdominal Symptoms score,

β_2 is the parameter estimate for the baseline VH:CD ratio,

ε_{ij} is the random error term for subject i from treatment group j.

The modelling results (ANOVA table, parameter estimates, estimated treatment effect, marginal (i.e. least squares) means estimates and results of the check of assumptions, i.e. the check of common variance assumption) will be tabulated and 95% confidence intervals added, where appropriate.

The common variance assumption check is done using Levene's test.

This analysis will be done on the mITT analysis set and repeated on the PP analysis set.

8.6.2.4 Subgroup analyses for secondary efficacy variables

Subgroup analysis will be done for all three secondary endpoints using the same subgroups as described in Section 8.6.1.6. The subgroup analyses for the secondary endpoints will be done on the mITT analysis set only. The same type of models as used for the secondary endpoints will also be fit separately for each level of the subgroup.

8.6.3 Other Efficacy Variable(s)

All other efficacy variables will be analyzed on mITT analysis set, if not specified otherwise. Tabulation by subgroups, where noted, is referring to the subgroups as specified for the subgroup analysis of primary and secondary efficacy variables.

CeD PRO non-GI Domain Scores (Headache and Tiredness Items)

Change from baseline through Week 24 in the CeD PRO non-GI domain scores (headache and tiredness items) will be tabulated by treatment group and by time point, both overall and by subgroups.

Mean change from baseline by treatment group and time point will be plotted, both overall and by subgroups.

CeD PRO Nausea Domain Scores

Change from baseline through Week 24 in the CeD PRO Nausea domain score will be tabulated by treatment group and time point, both overall and by subgroups.

Mean change from baseline by treatment group and time point will be plotted, both overall and by subgroups.

CeD PRO Symptomatic and Asymptomatic Days

Symptomatic (Score of greater than 0) and asymptomatic (Score of 0) days will be assessed in terms of the Abdominal Symptoms domain, Diarrhea and Loose Stool Domain, and Total GI score of the CeD PRO in a binary way.

In order to make the post-baseline number of symptomatic and asymptomatic days comparable with the baseline, the ratio of the total numbers to the overall number of days and the ratio of monthly numbers to the total number of days at each month through Week 24 will be summarized for each domain. Other cut off points for symptomatic scores including Score of ≥2 or Score of ≥3 in the domain scores will be evaluated.

MMRM analysis will be performed to assess changes from baseline through Week 24 on monthly totals of symptomatic days for each domain, with treatment, week, and week by treatment as fixed effects, the continuous baseline Abdominal Symptoms domain score and VH:CD ratio as covariates, and subject as a random effect. The model will be similar to that of the primary model.

Percent Change from Baseline in CeD PRO Domains

Percent change from baseline through Week 24 in the Abdominal Symptoms domain, the Diarrhea and Loose Stool domain, and the Total GI score of the CeD PRO will be summarized by treatment group and time point.

Proportion of Subjects Who Reach 30% and 50% Reduction in CeD PRO Domains

Subjects who reach a 30% and 50% reduction from baseline in the Abdominal Domain, Diarrhea and Loose Stool Domain, and Total GI score of the CeD PRO scores will be tabulated by counts and proportions for each week of the study, including tabulation overall and by subgroup. The proportions of these subjects at Week 24 will be analyzed with a chi-square test.

Weekly Worst Symptom Domain Score in CeD PRO

Absolute change from baseline through Week 24 in weekly worst symptom domain score for each of the following three domains (1) Abdominal Symptom domain, (2) Diarrhea and Loose Stool domain, and (3) Total GI score of the CeD PRO will be analyzed in a similar manner to that of the

primary endpoint, by using MMRM model with treatment, week, and week by treatment as fixed effects, the continuous baseline Abdominal Symptoms domain score and VH:CD ratio as covariates, and subject as a random effect.

The absolute values and change from baseline values (absolute and percent) will also be summarized by treatment group and time point.

Mean change from baseline of weekly worst symptom domain score will be plotted by treatment and time point for each domain.

BSFS Weekly Stool Frequency Type 6 or 7

Absolute change from baseline through Week 24 in total weekly stool frequency (sum of daily frequencies) for stools that are Type 6 or 7 based on the BSFS will be tabulated by treatment group and week. For imputation rules refer to Section 8.2.3.

Mean change from baseline of total weekly stool frequency of BSFS Type 6 or 7 will be plotted by treatment and time point.

Gluten-Induced Serum Antibodies

Absolute change from baseline through Week 24 will be tabulated by treatment group and time point (both overall and by subgroup) in the following gluten-induced serum antibodies for subjects who had all their samples analyzed through ELISA methods:

- Anti-tissue transglutaminase antibodies (anti-tTG) IgA
- Anti-deamidated gliadin peptide (anti-DGP) IgA

Anti-tTG IgG and Anti-DGP IgG are only collected at Screening and will be summarized as part of Baseline Characteristics.

Investigator Global Assessment (IGA)

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 (Inactive Disease, Mild Disease, Moderate Disease, Severe Disease, Very Severe Disease) at each specified time point. Absolute change from baseline to worst post-baseline IGA through Week 24 will be tabulated by treatment group in a shift table. Additionally, this table will be repeated for each subgroup.

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 placebo, 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."

The qualitative responses will be scored quantitatively as 1= Much better, 2 = A little better, 3 = No change, 4 = A little worse, 5 = Much worse for analysis.

Absolute change from baseline in PGIC through Week 24 will be tabulated by treatment and time point. Additionally, this table will be repeated for each subgroup.

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."

The qualitative responses will be scored quantitatively as 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Very Severe for analysis.

Absolute change from baseline in PGIS through Week 24 will be tabulated by treatment and time point. Additionally, this table will be repeated for each subgroup.

PROACTIVE Dietary Questionnaire

The dietary questionnaire relates to subject's celiac disease during the past 7 days. Subjects will answer the following two questions weekly from Visit 1:

- How many days did you consume a meal prepared outside of your home?
- How many days do you think you consumed gluten?

The results will be summarized by treatment group and week based on the visit windowing for the PROACTIVE Dietary Questionnaire. The results will also be presented in a data listing.

Impact of Celiac Disease Symptoms Questionnaire (ICDSQ)

The ICDSQ questionnaire is an instrument developed by Alvine Therapeutics to assess the impact of celiac disease symptoms on patients' quality of life (Acaster and Acaster, 2011).

For each question, the qualitative assessments will be scored quantitatively as 1 = Not at all, 2 = A Little, 3 = Moderately, 4 = Very Much, 5 = Completely for analysis.

Absolute change from baseline through Week 24 in domains of the ICDSQ (Daily Activities, Social Activities, Emotional Well-Being, Physical Activities) and Total score will be summarized by treatment and time point.

The scoring of the ICDSQ domains (ICDSQ Scoring Manual v1.0, April 2022) is as follows:

- Daily Activities: Mean of Items 1 through 4
- Social Activities: Mean of items 5 through 7
- Emotional Well-Being: Mean of items 8 through 12
- Physical Activities: Mean of items 13 and 14

The total ICDSQ score is calculated as the sum of the four domain scores.

EQ-5D-5L

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).

Absolute change from baseline through Week 24 in EQ-5D-5L (VAS score) will be tabulated by treatment group and time point, both overall and by subgroups.

Descriptive system items will be listed.

Disease Activity Biomarkers

Blood samples to analyze biomarkers of disease activity (e.g., serum IL-15) will be collected prior to treatment administration on visits 3, 5, 7, 9, 11, 13, 15 and 16. Absolute change from baseline through Week 24 in biomarker of disease activity (serum IL-15) will be tabulated by treatment group and time point.

Small Bowel Mucosal Architecture as Assessed by VH:CD Ratio

EGD and biopsy are performed at visits 2 and 15. Villus height (VH, in micrometers) and crypt depth (CD, in micrometers) and their ratio, VH:CD will be assessed. Absolute change from baseline to Week 24 in small bowel mucosal architecture, as assessed by the change in VH:CD in intestinal biopsies will be tabulated by treatment group. Additionally, tabulations of proportion (%) of subjects with VH:CD <2 and ≥ 2 at baseline and end of study will be provided.

Marsh-Oberhuber Histology Score

The Marsh-Oberhuber histology score (M0, M1, M2, M3a, M3b, or M3c) will be assigned from EGD biopsy samples collected at visits 2 and 15. The Marsh-Oberhuber histology scale will be assessed as frequencies and proportions. Frequencies will be tabulated for each category on the scale, along with respective change from baseline in a shift table.

Additionally, a 3-category outcome will be derived, in which subjects are categorized as having worsening scores from baseline, no change from baseline, and those with improvement from baseline. Marsh score of 0 is considered the best and Marsh score of 3c is considered the worst. Any score shifts in the direction from 0 towards 3c (e.g. 0 to 1 or 3a to 3b) is considered worsening. On the other hand, any score shifts from the direction from 3c to 0 is considered as improvement (e.g. 3c to 3b, or 2 to 0 is considered improvement).

The 3-category outcome will be summarized by treatment group. The Cochran–Mantel–Haenszel test (CMH) (using modified ridit scores for the 3-level outcome), stratified by baseline Marsh-Oberhuber score (M0, M1, M2 vs. M3a, M3b, M3c) will be used to assess differences between active and placebo treatments in this 3-category outcome.

Adherence to GFD

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.

The G12 stool test and urine gluten test results (positive/negative) will be presented by treatment group and visit. Additionally, an overall summary of subjects will be generated, cross-tabulating the baseline test result (positive/negative) with having at least one post-baseline test (positive/negative), separately for urine and stool tests.

8.7 Analysis of Safety and Tolerability

All analyses of safety and tolerability will be conducted on Safety analysis set, if not specified otherwise.

8.7.1 Extent of Exposure

The number and percentage of subjects who received 0, 1, 2, 3, or 4 injections at each visit will be summarized by treatment group.

Dates and times of subcutaneous (SC) injections will be listed by subject.

Additionally, the number and percentage of subjects who received 0, 1, 2, 3, or 4 injections at each visit will be summarized for the run-in period using the RIS analysis set.

The dates and times of the subcutaneous (SC) injections during the run-in period will be listed by subject.

8.7.2 Adverse Events

Adverse Events (AEs) and serious adverse events (SAEs) are collected from the signing of the ICF until final visit (Visit 16) and will be classified by System Organ Classes (SOC) and Preferred Terms (PT) using the latest MedDRA dictionary applicable at the time of database lock.

Treatment-emergent adverse events (TEAEs) are collected from the first dose of double-blind study drug until the last dose of double-blind study drug + 42 days. The AEs and SAEs reported during the screening period (those which started after the first screening visit and ended before the start of run-in period or ongoing at the time of run-in period) and single-blind placebo run-in period AEs and SAEs (those which started after visit 1 (first run-in period visit) and ended before the start of double-blind randomized treatment period or ongoing) will be reported separately from the TEAEs.

AEs reported during post-treatment period, i.e. starting at the end of treatment emergent period will be summarized by System Organ Classes (SOC) and Preferred Terms (PT).

Injection site reactions are those identified programmatically using the MedDRA High Level Term of "Injection site reactions".

Adverse Events of Special Interest (AESI) are (1) severe opportunistic infections and (2) hypersensitivity reactions of at least moderate severity. AESI will be programmatically identified for summarization based on the criteria below using MedDRA Preferred Term or Standardized MedDRA Queries (SMQ) (narrow) which also meet severity/seriousness criteria in the eCRF:

Table 3 AESI Criteria

AESI Category	eCRF AE page	MedDRA Search Terms
Severe opportunistic infections	"Severe" or Serious noted in eCRF	PT included in SMQ (narrow) of • Opportunistic infections (SMQ) (20000235)
Hypersensitivity reactions of at least moderate severity	"Moderate", "Severe", or Serious noted in eCRF	PT contains "Hypersensitivity" or "hypersensitivity" OR PT included in SMQ (narrow) of • Anaphylactic reaction (SMQ) (20000021) • Hypersensitivity (SMQ) (20000214) • Severe cutaneous adverse reactions (SMQ) (20000020) • Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ) (20000225) • Angioedema (SMQ) (20000024)

An overall summary table of treatment-emergent adverse events will be produced and will present the number and proportion (%) of subjects in each treatment group who have at least one adverse event in the following categories:

- TEAE
- TEAE related to study drug (possible, probable, or definite attribution)
- TEAE severity (mild, moderate, severe)
- TEAE leading to study treatment discontinuation
- TEAE leading to death
- Treatment-emergent injection site reactions
- Treatment-emergent SAE
- Treatment-emergent AESI

In case of more than one reported severity (e.g., mild, moderate, severe) and/or causality (e.g., unrelated, unlikely, possible, probable, definite) the worst outcome is used for reporting, respectively.

Summary tables presenting the number and proportion (%) of subjects in each treatment group who have at least one adverse event in the following categories will be presented by SOC and PT:

- TEAE
- AEs occurring during the Screening period (All Screened analysis set)
- AEs occurring during the Run-in period (Run-in analysis set)
- TEAE related to study drug (possible, probable, or definite attribution)
- Severe TEAE
- TEAE leading to study treatment discontinuation
- TEAE leading to death

- Treatment-emergent injection site reactions
- Treatment-emergent SAE
- SAE occurring during the Screening period (All Screened analysis set)
- SAE occurring during the Run-in period (Run-in analysis set)
- Treatment-emergent AESI

For the summaries of severe TEAE, serious TEAE, treatment-emergent AESI, and TEAE leading to study treatment discontinuation, the risk differences (comparing PRV-015 arms to placebo) and exact 95% CI (using the Clopper-Pearson method) will be provided for each SOC or PT.

A summary table presenting the number and proportion (%) of subjects in each treatment group who have at least one TEAE will be presented by descending frequency of PT.

For summary tables by SOC/PT or by PT, subjects will be counted once in the applicable row.

Data listings will also be provided for AEs and SAEs occurring during Screening and Run-in periods, respectively. Additional data listings of TEAEs will be provided.

8.7.3 Clinical Laboratory Tests

8.7.3.1 Serum Chemistry, Hematology, Urinalysis, Pregnancy Tests

Laboratory safety variables include hematology, clinical chemistry and urinalysis panels. The complete list of laboratory tests is included in Table 4 below.

Table 4. Clinical Laboratory Tests

Serum Chemistry (Units)	Hematology (Units)	Urinalysis
ALT (IU/L)	Basophils (10^9/L)	Appearance
AST (IU/L)	Basophils/Leukocytes (%)	Bilirubin
Albumin (g/L)	Eosinophils (10^9/L)	Color
Alkaline Phosphatase (IU/L)	Eosinophils/Leukocytes (%)	Glucose
Total Bilirubin (umol/L)	Mean cell hemoglobin (MCH)	Ketones
Direct Bilirubin (umol/L)	Mean Corpuscular HGB Concentration	Leukocyte Esterase
Calcium (mmol/L)	(g/L)	Nitrite
Carbon Dioxide (mmol/L)	Mean Corpuscular Hemoglobin (fmol)	Occult Blood
Chloride (mmol/L)	Mean Corpuscular Volume (fL)	pH
Creatinine (umol/L)	Hematocrit (%)	Protein
Glucose (mmol/L)	Hemoglobin (g/L)	Specific Gravity
Magnesium (mmol/L)	Lymphocytes (10^9/L)	Urobilinogen
Phosphorus (mmol/L)	Lymphocytes/Leukocytes (%)	
Potassium (mmol/L)	Monocytes (10^9/L)	Urine Microscopic
Total Protein (g/L)	Monocytes/Leukocytes (%)	
Sodium (mmol/L)	Neutrophils (10^9/L)	Urine pregnancy
Urea Nitrogen (mmol/L)	Neutrophils/Leukocytes (%)	test
	Platelets (10^9/L)	
	Red Blood Cell Count (10^{12}/L)	

	White Blood Cell Count (10^9/L)	

Clinical laboratory parameters will be obtained at times indicated in the SoA in Appendix 11.1. Cut-off values considered to be potentially clinically important (PCI) for selected laboratory tests are outlined in Appendix 11.2.

A summary of subjects meeting any of the PCI criteria for post-baseline laboratory measurements will be provided by treatment group. All clinical laboratory test results will be provided in data listings with PCI criteria flagged.

Separate data listings for urine and serum pregnancy tests will be provided in female subjects of childbearing potential.

Potential Hy's law (ALT or AST > 3 x ULN concurrent with total bilirubin > 2 x ULN at the same visit) will be summarized by treatment group and listed. eDish plots will be used to present subjects potentially meeting Hy's law.

8.7.3.2 Ferritin, Iron, TIBC, Vitamin D, Vitamin B12, Folate

Blood samples for Ferritin, Iron, TIBC, Vitamin D, Vitamin B12, and Folate are collected at Visits 3, 9, and 15.

The results from these tests will be provided in data listings.

8.7.3.3 Serum IgA

The results of the Serum IgA test at Screening will be provided in a data listing.

8.7.3.4 GGT

GGT is tested in the event ALP is >3 x ULN. The results of any applicable GGT testing will be presented in a data listing.

8.7.3.5 HbA1c

Subjects who have a history of Type 1 or Type 2 diabetes or subjects who present with glucose detection in urine should have HbA1c tested on study. The HbA1c results will be presented in a data listing.

8.7.4 Other Safety Variables

8.7.4.1 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.

Descriptive statistics will be provided by visit and treatment group for all vital sign parameters. All vital signs will be further provided in a data listing.

A separate data listing will be provided showing all vital signs for subjects where a vital sign has met PCI criteria.

Cut-off values considered to be potentially clinically important (PCI) for vital signs are outlined in Appendix 11.3.

8.7.4.2 Weight

Descriptive statistics will be provided by visit and treatment group for body weight (kg). Means of both the absolute values and changes from baseline in weight will be presented graphically by visit and treatment group. Cut-off values considered to be potentially clinically important (PCI) for weight is outlined in Appendix 11.3.

8.7.4.3 Physical Examination

Physical examination results will be listed by treatment group, visit, body system, result (normal, abnormal, not done) and clinical significance (yes, no).

A separate data listing will be provided showing all physical examination results for subjects who experienced at least one abnormal and clinically significant result.

8.8 Pharmacokinetics and Immunogenicity

Blood samples for PK and anti-drug antibodies (ADA) will be collected before study drug administration (baseline) and at each visit before dosing (trough).

8.8.1 Pharmacokinetics

All analyses will be conducted using SAS version 9.4 or higher. All derivations, statistical analyses, summaries and listings will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared using the same versions of SAS, or Phoenix® WinNonlin® 8.3 or higher (Certara, L.P. Princeton, New Jersey, United States of America [USA]).

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

8.8.1.1 Serum Concentration Data

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry.

A listing of PK blood sample collection times will be provided. Serum concentrations will be summarized using descriptive statistics by time point for PRV-015 treatment groups. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Descriptive statistics for concentration time data will include n, mean, standard deviation (SD), median, Lower Quartile, Upper Quartile, minimum, maximum, Geometric mean and Geometric Coefficient of Variation (GCV). For the reporting of descriptive statistics, the mean, standard deviation and Geometric mean will be presented to one digit more precision than the source data. The minimum, median, maximum, Lower Quartile and Upper Quartile will be presented to the same precision as the source data. Geometric Coefficient of Variation will always be reported to 1 decimal place. A minimum of n=3 is required for all descriptive statistics to be generated. If n is less than 3, only N, n, minimum, and maximum will be reported.

A subject listing of all concentration time data for each treatment will be presented. Figure of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for PRV-015 treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

No imputations will be done for missing data. Individual concentrations will be reported to the same precision as the source data.

8.8.1.2 Pharmacokinetic Analysis

Pharmacokinetic analysis will be done on PK analysis set.

PRV-015 trough concentrations (C_{min}) is the trough concentration which will be the pre-dose concentration for respective visits. PRV-015 trough concentrations (C_{min}) will be summarized using descriptive statistics by time point for PRV-015 treatment groups. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Descriptive statistics for concentration time data will include n, mean, standard deviation (SD), median, Lower Quartile, Upper Quartile, minimum, maximum, Geometric mean and Geometric Coefficient of Variation (GCV). For the reporting of descriptive statistics, the mean, standard deviation and Geometric mean will be presented to one digit more precision than the source data. The minimum, median, maximum, Lower Quartile and Upper Quartile will be presented to the same precision as the source data. Geometric Coefficient of Variation will always be reported to 1 decimal place. A minimum of n=3 is required for all descriptive statistics to be generated. If n is less than 3, only N, n, minimum, and maximum will be reported.

In addition, dose proportionality, achievement of steady-state, and accumulation ratio based on C_{min} will be assessed.

Dose Proportionality:

Dose proportionality of C_{min} will be assessed separately for PK sampling Day 15 (Visit 4) and Day 169 (Visit 15) using the power model ($C_{min}= \alpha * Dose^{\beta}$), along with an "estimation" interpretation, according to the recommendations in Gough et al. (1995). The power model will be fitted on the log-transformed scale as:

$$\log(Y_i)=\alpha + \beta*\log(Dose_i)+\varepsilon_i,$$

where Y_i and $Dose_i$ are the C_{min} value and dose value for subject i, respectively, ε_i is the random error, α is the intercept parameter and β is the slope parameter. The power model parameters will be estimated using least -squares (LS) regression and presented with 90% CIs. Model lack-of-fit will be assessed by residual plots, and by an F-test of the residual mean square versus the pure error residual mean square. If the model fit is adequate, point estimate and 90% CI for β will be obtained, and used to obtain point estimates and 90% CIs for the increase in C_{min} associated with an r-fold (r = 2 and r = high dose / low dose) increase in dose, by exponentiating r to the power of the β point estimate and confidence limits, $r^{\beta \pm t \times SE(\beta)}$. If there is evidence of model lack-of-fit, then an ANOVA model on the log-transformed C_{min} with dose as fixed categorical effect will be used. Point estimate and 90% CI, associated with mean difference between pairwise dose increases, obtained from this model will be converted back to the original scale using the antilog transformation.

Accumulation ratio:

For C_{min}, individual accumulation ratio Rac C_{min} at Day 169 will be calculated as C_{min} at Day 169/C_{min} at Day 15. A listings of individual accumulation ratios will be provided, along with their descriptive statistics (arithmetic mean, standard deviation, geometric mean, coefficient of variation (%), median, minimum and maximum).

Accumulation versus Day 15 (Visit 4) will be assessed for Day 169 (Visit 15) using an ANOVA model on the log-transformed accumulation ratio (Rac C_{min}) with dose as fixed categorical effect. Point estimates and 90% CI obtained, by dose level and overall, from this model will be converted back to the original scale using the antilog transformation.

Achievement of steady-state:

Steady state on Cmin (ie, Ctrough) will be assessed using a nonlinear mixed model (Hoffman et al, 2005):

$$C_{ij} = C_{ss}e^{c_i}(1 - e^{-(\gamma e^{g_i} j)})e^{\varepsilon_{ij}}$$

where C_{ij} is the observed trough (C_{min}) plasma concentration for the i^{th} subject on Day j, C_{SS} is the average steady state trough (C_{min}) plasma concentration, γ is the average first-order elimination rate, $\varepsilon_{ij} \sim N(0, \sigma^2_e)$ is the random within-subject error, and c_i and g_i are the random individual deviations from C_{ss} and γ, respectively, such that

$(c_i, g_i) \sim N([0, 0], \Sigma)$ with

$$\Sigma = \begin{bmatrix} \sigma_c^2 & \sigma_{cg} \\ \sigma_{cg} & \sigma_g^2 \end{bmatrix}$$

The model assumes a log-normal distribution for both the within-subject erros (ε_{ij}) and the random effects c_i and g_i. The above nonlinear model analysis will be based on the log-transformed C_{min} values. Data from all subjects together from all dose groups will be used for the analysis.

Time (t_{ss} in days) at which 90% of the subject-specific C_{ss} is achieved (ie, individual steady state attainment) will be calculated from the model, using the equation:

$$t_{ss} = \frac{\log(1 - 0.9)}{-\gamma}$$

Similarly, time (in days) at which 50% of the subject-specific C_{ss} is achieved (ie, average steady state attainment) will also be provided.

In addition, model parameter estimates with standard errors and 90% CIs will be provided. The adequacy of the nonlinear model will be assessed graphically by plotting residual versus dose, residual versus time, and observed (log-scale) and predicted values versus time for individual subjects.

8.8.2 Immunogenicity

Immunogenicity, i.e. the generation of ADA, will be tested in an immunoassay. Samples that test positive for binding antibodies will be then tested in an assay to detect neutralizing antibodies (NAb). Immunogenicity will be tabulated by treatment group, visit, ADA test result (negative, positive) and neutralizing antibodies test result (negative, positive) and listed using the IMG analysis set.

8.9 Interim Analyses and Data Monitoring

No formal interim analysis is planned for this study. An internal Data Monitoring Committee (DMC) evaluated risk-benefit continually during the study and did not recommend any changes to study conduct.

8.10 Changes in the Statistical Plans from Those Presented in the Study Protocol (if applicable)

The following list of changes are applicable to this SAP and differ from those presented in the study protocol:

- For general summaries of continuous values, Q1 and Q3 will be presented in addition to N, mean, SD, median, minimum, and maximum. Coefficient of variation (CV%) will not be presented for general summaries, but $CV\%_{geo}$ will be provided for PK-related summaries as described.
- The study protocol indicates that the primary efficacy model will test an AR(1) variance-covariance structure against the Unstructured variance-covariance structure using likelihood

ratio testing. The SAP removes this testing and instead provides a hierarchy of variance-covariance structures to use in the case of issues with model convergence.

- Change from baseline at 24 weeks for the CeD PRO Nausea domain has been added as an exploratory endpoint.
- The protocol specifies that exploratory clinical endpoints will be evaluated on the Per Protocol analysis set. This SAP indicates that only the primary and secondary efficacy endpoints will be evaluated on the Per Protocol analysis set; however, exploratory analyses may be conducted on the Per Protocol analysis set as necessary.
- Due to an unexpected change in laboratory platform, the tertiary Anti-TTG antibody IgA and Anti-DGP antibody IgA analyses will be limited to the subset of subjects who have all of their available samples analyzed via ELISA methods.
- The Protocol specifies that primary analysis will be done on ITT population, in this SAP mITT population has been defined and all efficacy analysis will be done on mITT population unless otherwise specified.

8.11 Execution of Statistical Analyses

Statistical analysis will be performed by IQVIA Biotech (formerly StatFinn) under the supervision of Provention Bio, Inc.

9 HARDWARE AND SOFTWARE

Statistical analysis, tables, figures and subject data listings will be performed with SAS® for Windows version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

10 REFERENCES

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11 APPENDICES

11.1 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=lutenizing 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.

11.2 PCI criteria for Hematology, Serum Chemistry, Urinalysis

		Conventional Units			SI Units		
Test Name	Sex	Reference Range	Units	PCI Criteria	Reference Range	Units	PCI Criteria
Hematology							
Hemoglobin	M	13.5 – 17.5	g/dL	< 8.1 or > 20	135 - 175	g/L	< 81 or > 200
	F	12.0 – 15.5	g/dL	< 8.1 or > 20	120 - 155	g/L	< 81 or > 200
Hemoglobin				2 point decrease from baseline			20 point decrease from baseline
White Cell Count		4.0 – 11.0	x10E3/uL	< 2.1 or > 35	4.0 - 11.0	x10E9/L	< 2.1 or > 35
Eosinophils (Abs)		0.0 - 0.6	x10E3/uL	>=3	0.0 - 0.6	x10E9/L	>=3
Neutrophils (Abs)		1.5 - 7.7	x10E3/uL	< 1	1.5 - 7.7	x10E9/L	<1
Platelets		150 - 450	x10E3/uL	< 100 or > 1000	150 - 450	x10E9/L	< 100 or > 1000
Serum Chemistry							
Protein (Total)	M	5.9 - 8.0	g/dL	< 4.0	59 – 80	g/L	< 40
	F	6.2 – 7.9	g/dL	< 4.0	62 - 79	g/L	< 40
Albumin	M	4.03 - 5.51	g/dL	< 2.0	40.3 – 55.1	g/L	< 20
	F	4.02 – 5.24	g/dL	< 2.0	40.2 – 52.4	g/L	< 20
ALT	M	6.7 – 33.4	IU/L	>=3X ULN	6.7 – 33.4	IU/L	>=3X ULN
	F	6.6 – 22.9	IU/L	>=3X ULN	6.6 – 22.9	IU/L	>=3X ULN
AST	M	12.4 – 33.0	IU/L	>= 3X ULN	12.4 – 33.0	IU/L	>= 3X ULN
	F	11.8 – 25.7	IU/L	>= 3X ULN	11.8 – 25.7	IU/L	>= 3X ULN
AP (AlkPhos)	M	36.1 – 124.2	IU/L	>= 3XULN	36.1 – 124.2	IU/L	>= 3XULN
	F	35.6 – 118.3	IU/L	>= 3XULN	35.6 – 118.3	IU/L	>= 3XULN
Bilirubin (Total)	M	0.24 – 1.49	mg/dL	>=2X ULN	4.10 – 25.48	umol/L	>=2X ULN
	F	0.19 – 1.13	mg/dL	>=2X ULN	3.25 – 19.32	umol/L	>=2X ULN

		Conventional Units			SI Units		
Test Name	Sex	Reference Range	Units	PCI Criteria	Reference Range	Units	PCI Criteria
Bicarbonate	M	20 - 32	mmol/L	< 18 or > 40	20 - 32	mmol/L	< 18 or > 40
	F	19 - 29	mmol/L	< 18 or > 40	19 - 29	mmol/L	< 18 or > 40
BUN (Urea)	M	8.2 – 23.8	mg/dL	> 40	2.93 – 8.50	mmol/L	>14.25
	F	5.9 – 21.4	mg/dL	> 40	2.11 – 7.64	mmol/L	>14.25
Calcium	M	8.5 - 10.3	mg/dL	< 6 or > 12	2.13 - 2.58	mmol/L	< 1.5 or > 3
	F	8.5 – 10.2	mg/dL	< 6 or > 12	2.13 – 2.55	mmol/L	< 1.5 or > 3
Chloride	M	98 – 108	mmol/L	< 90 or > 125	90 – 108	mmol/L	< 90 or > 125
	F	99 - 107	Mmol/L	< 90 or > 125	99 - 107	mmol/L	< 90 or > 125
Creatinine	M	0.63 – 1.20	mg/dL	>=1.5	55.69 – 106.08	umol/L	>=132
	F	0.51 – 0.96	mg/dL	>=1.5	45.08 – 84.86	umol/L	>=132
Glucose		< 140	mg/dL	> 500	< 7.8	mmol/L	> 27.75
Magnesium	M	1.8 – 2.2	mg/dL	<1.22 or >4.87	0.74-0.90	mmol/L	<0.5 or >2
	F	1.7 – 2.2	mg/dL	<1.22 or >4.87	0.70 – 0.90	mmol/L	<0.5 or >2
Phosphate	M	2.1 - 4.6	mg/dL	< 0.5	0.68 – 1.49	mmol/L	< 0.5
	F	2.4 – 4.8	mg/dL	< 0.5	0.78 – 1.55	mmol/L	< 0.5
Potassium	M	3.8 – 4.9	mmol/L	< 3 or > 6	3.8 – 4.9	mmol/L	< 3 or > 6
	F	3.7 – 5.2	mmol/L	< 3 or > 6	3.7 – 5.2	mmol/L	< 3 or > 6
Sodium		138 - 144	mmol/L	< 125 or > 160	138 - 144	mmol/L	< 125 or > 160

Urinalysis						
Amorphous Crystals			n/a			n/a
Bacteria	Negative		Numerous	Negative		Numerous
Bilirubin	Negative		3+	Negative		3+

Crystals	Negative		Numerous	Negative		Numerous
Epithelial Cells	0 - 5	HPF	Numerous	0 - 5	HPF	Numerous
Glucose (Urine)	Negative		3+	Negative		3+
Granular Casts	None	LPF	>0	None	LPF	>0
Hemoglobin (Urine)	Negative		3+	Negative		3+
Hyaline Casts	0 - 1	LPF	>1	0 - 1	LPF	>1
Ketones	Negative		3+	Negative		3+
Leucocyte Esterase	Negative		3+	Negative		3+
Nitrite	Negative		3+	Negative		3+
pH	5.0 - 8.0		n/a	5.0 - 8.0		n/a
Protein (Total) (Urine)	Negative		3+	Negative		3+
RBC	0 - 2	HPF	>=10	0 - 2	HPF	>=10
RBC Casts	None	LPF	>0	None	LPF	>0
Sp. Gravity (SG)	1.015 - 1.025		n/a	1.015 - 1.025		n/a
Urobilinogen	Negative		3+	Negative		3+
Waxy Casts	None	LPF	>0	None	LPF	>0
WBC	0 - 5	HPF	>=10	0 - 5	HPF	>=10
WBC Casts	None	LPF	>0	None	LPF	>0

11.3 PCI criteria for Vital Signs and Weight

Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

11.4 SAS Codes

Primary model:

```
proc glimmix data = data;
   class USUBJID TRT(ref = 'Placebo') Week(ref = FIRST);
   model CHANGE = TRT WEEK TRT*WEEK BASEABD BASEVHCD/ solution;
   random _residual_ / subject = USUBJID type = UN;

   lsmeans TRT TRT*WEEK /diff cl alpha=0.05;
   ods output LSMeans = LSMeans2;
Ods output diffs = diffs1;
run;
```

Note that the value of type will be changed according to which covariance structure is being fitted (UN).

Multiple Imputation

Step 0. Determine missing patterns in the data

```
proc mi data=data nimpute = 0 ;
var BASE week2-week24;
ods select misspattern;
run;
```

Step 1. Generation of imputed datasets:

```
Proc mi data = data seed=44853 nimpute=100 out=new_data;
By TRT;
MCMC impute = MONOTONE;
var BASE week2-week24;
run;

%macro miseq(in=,imputed=,seed=,missing=,out=);
proc mi data=&in. seed=14823 nimpute=1 out=&out.;
class TRT;
by _Imputation_;
monotone reg ( &missing. = BASE &imputed. TRT vhcd/details);
mnar model(  &imputed.  &missing. / modelobs= NCMV);
var BASE TRT vhcd &imputed. &missing. ;

run;
%mend;

%miseq(in=new_data, imputed =, seed = 1261, missing = week2, out =
new_data1);
%miseq(in=new_data1, imputed = (Base, week2), seed = 44853, missing =
week4, out = new_data2)
Etc..
Continue until week 24.
```

Imputation using placebo subjects at the same visit (used for imputation of intercurrent events (presence of gluten))

```
proc mi data=new_data seed=14823 nimpute=1 out=outex15;
class flag;
by _Imputation_;
monotone reg (/details);
mnar model(  week2-week24 / modelobs= (flag = '1'));
var BASE week2-week24;
run;

/*flag = 1 is for those placebo subjects which did not experience any
presence of gluten*/
```

Step 2. Model-based analysis using each imputed dataset

```
proc glimmix data=new_data2;
   class USUBJID TRT(ref='Placebo') WEEK(ref=FIRST);
   model CHANGE = TRT WEEK TRT*WEEK BASEABD BASEVHCD/ solution;
   by _imputation_;
   random _residual_ / subject=USUBJID type=UN;
  lsmeans TRT TRT* WEEK / diff cl alpha=0.05 cl;
          ods output LSMeans=LSMeans2;
   ods output diffs=diffs1;
run;
```

Step 3. Pooling the results from each model-based analysis

```
proc mianalyze data = lsmeans2;
   by TRT Week;
   modeleffects estimate;
   stderr stderr;
   ods output ParameterEstimates=milsmean;
run;


data diff2;
   set diffs1;
   comparison = TRT||' vs '||left(_TRT);
   where _Week = 'Placebo' and Week =_Week;
run;


proc mianalyze data = diff2;
   by comparison Week;
   modeleffects estimate;
   stderr stderr;
   ods output parameterestimates=midiff;
run;
```

Analysis of covariance (ANCOVA)

(IEL Density)

```
proc glm data = data alpha=0.05 outstat = F_tests;
   class TRT(ref='Placebo');
   model CHANGE = TRT BASEABD BASEVHCD/ clparm solution SS1 SS2;
   estimate "PRV-015 100 mg vs Placebo" TRT 1 0 0 -1;
   estimate "PRV-015 300 mg vs Placebo" TRT 0 1 0 -1;
   estimate "PRV-015 600 mg vs Placebo" TRT 0 0 1 -1;
   lsmeans TRT /cl stderr alpha=0.05 pdiff = all;
   ods output ParameterEstimates=Par_est LSMeanCL=LS_meanCL
      LSMeans=LS_mean OverallANOVA=ANOVA Estimates=Eff_est;
run;
```

Levene's test

```
proc glm data = data alpha = 0.05;
   class TRT;
   model CHANGE = TRT  / clparm solution SS1 SS2;
   means TRT / hovtest;
   ods output HOVFTest = Levene;
run;
```

Chi-square test:

```
proc freq data = data;
   tables TRT*REDUCBLX / chisq;
   output out=CHiSqData pchi;

run;
```

where REDUCBLX shows if subject had X% reduction from baseline at Week 24.

The Cochran–Mantel–Haenszel test (CMH)

```
proc freq data=data;
   tables BLMED*TRT*RESPONSE / cmh scores=modridit;
   output out=outdata;
run;
```

where BLMED is baseline Marsh-Oberhuber score (M0, M1, M2 vs. M3a, M3b, M3c) score and RESPONSE shows if subjects have worsening scores.

12 DOCUMENT HISTORY

Version number	Version date	Status	Author
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0.3	19JUN2020	Draft	
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[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style [redacted] Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/30/2024 3:42:24 PM Viewed: 10/30/2024 4:02:20 PM Signed: 10/30/2024 4:03:00 PM
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[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/30/2024 3:42:25 PM Viewed: 10/30/2024 3:43:41 PM Signed: 10/30/2024 3:45:37 PM
Electronic Record and Signature Disclosure: Accepted: 3/28/2024 9:04:43 AM [redacted] Company Name: IQVIA		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
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Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	10/30/2024 3:42:25 PM
Certified Delivered	Security Checked	10/30/2024 3:43:41 PM
Signing Complete	Security Checked	10/30/2024 3:45:37 PM
Completed	Security Checked	10/31/2024 4:25:14 AM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

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