Title: A Phase 1, Four-Part Study to Assess the Safety, Tolerability, Pharmacokinetics, and Gluten Degradation Activity of PvP001, PvP002, and PvP003 in Healthy Adult Volunteers and to Assess the Safety, Tolerability, and Pharmacokinetics of PvP001 and PvP002 in Adults with Celiac Disease

NCT Number:NCT03701555

Protocol Approve Date: December 15, 2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Millennium Pharmaceuticals, Inc.

CLINICAL PROTOCOL

Amendment 6

Effective Date: December 15, 2020

PROTOCOL NUMBER: PvP-102-01

A PHASE 1, FOUR-PART STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND GLUTEN DEGRADATION ACTIVITY OF PVP001, PVP002, AND PVP003 IN HEALTHY ADULT VOLUNTEERS AND TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMAKOKINETICS OF PVP001 AND PVP002 IN ADULTS WITH CELIAC DISEASE

Development Phase: Phase 1

SPONSOR:

Millennium Pharmaceuticals, Inc. (Millennium), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA USA 02139
USA

Takeda Development Center Americas, Inc. and Millennium Pharmaceuticals, Inc. are wholly owned subsidiaries of Takeda Pharmaceutical Company Limited.

SPONSOR SIGNATURE PAGE

PPD

Date

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Clinical Study Title: A Phase 1, Four-Part Study to Assess the Safety, Tolerability, Pharmacokinetics, and Gluten Degradation Activity of PvP001, PvP002, and PvP003 in Healthy Adult Volunteers and to Assess the Safety, Tolerability, and Pharmacokinetics of PvP001and PvP002 in Adults with Celiac Disease

Protocol Number: **PvP-102-01**

Printed Name of Investigator: _____

Printed Institution Name & Address: _____

_____

_____

_____

I agree to conduct this study in accordance with the requirements of this Clinical Study Protocol and also in accordance with the following:

- To assume responsibility for the proper conduct of the study at this site;
- To conduct the study in compliance with this protocol, with any future amendments, and with any other study conduct procedures provided by Millennium Pharmaceuticals, Inc. or designee. I also agree to comply with good clinical practices (GCPs) and all regulatory requirements;
- Not to implement any change to the protocol without agreement from Millennium Pharmaceuticals, Inc. or designee and prior review and written approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard to the subject or for administrative aspects of the study (where permitted by all applicable regulatory requirements);
- That I am thoroughly familiar with the appropriate use of the investigational and approved product(s), as described in this protocol, and with any other relevant information (e.g., the Investigator's Brochure [IB]);
- To ensure that all persons assisting me with the conduct of this study are adequately informed about the investigational product(s) and about their study-related duties and functions as described in this protocol;
- That I am aware that certain regulatory authorities require Investigators to disclose all information about ownership interests and financial ties related to the Sponsor and/or the investigational product(s). Consequently, I agree to supply all such information to Millennium Pharmaceuticals, Inc. and to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study. I also agree that Millennium Pharmaceuticals, Inc. may disclose any information it has regarding ownership interests and financial ties to regulatory authorities.

_____ _____

Signature of Investigator Date

STUDY PERSONNEL AND CONTACTS

Sponsor:

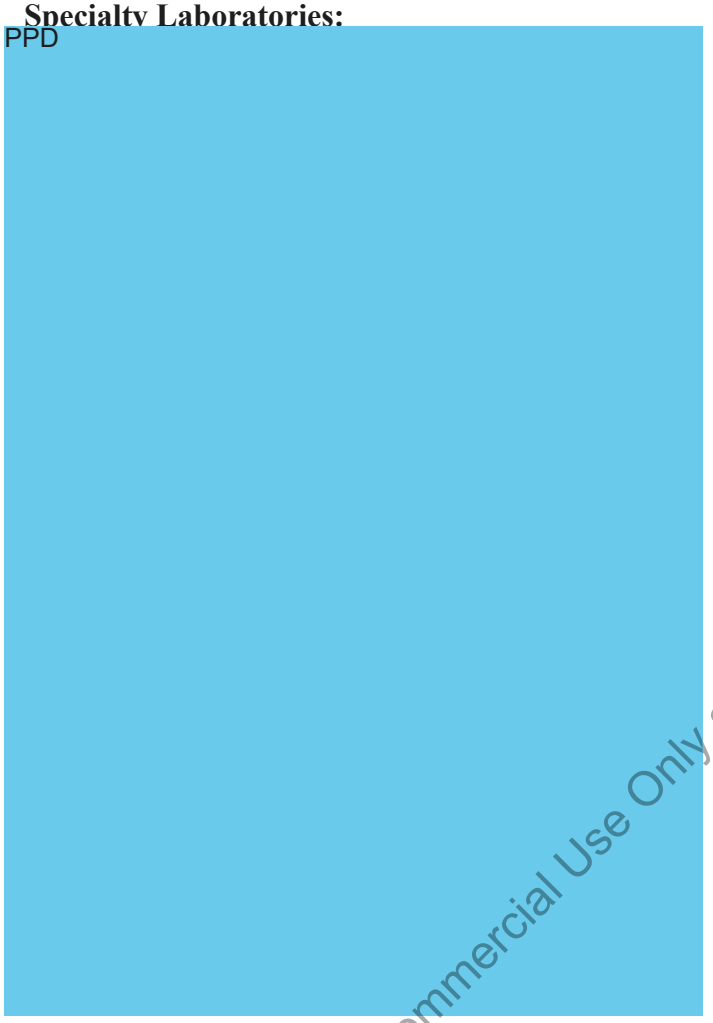
Millennium Pharmaceuticals, Inc. **(Millennium), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited**
40 Landsdowne Street
Cambridge, MA USA 02139
PPD

Medical Monitor:
PPD

Serious Adverse Event Reporting:
PPD

Data Management and Biostatistics:
PPD

Specialty Laboratories:



SYNOPSIS

Name of Sponsor: Millennium Pharmaceuticals, Inc. (Millennium), a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Investigational Products: PvP001, PvP002, PvP003

Reference Compound: Placebo, comparator (sterile water)

Title of Study: A Phase 1, Four-Part Study to Assess the Safety, Tolerability, Pharmacokinetics, and Gluten Degradation Activity of PvP001, PvP002, and PvP003 in Healthy Adult Volunteers and to Assess the Safety, Tolerability, and Pharmacokinetics of PvP001and PvP002 in Adults with Celiac Disease

Protocol Number: PvP-102-01

Phase of Development: Phase 1

Number of Study Centers: This is a single center study

Objectives:

Part 1

Primary Objective:

- To determine the safety and tolerability of single doses of PvP001 and PvP002 in healthy volunteers and patients with celiac disease (CeD)

Secondary Objectives:

- To determine the pharmacokinetics (PK) of PvP001 and PvP002 in healthy volunteers and patients with CeD
- To determine the maximum tolerated dose (MTD) (100, 300, or 900 mg) of PvP001 in healthy volunteers for use in Part 2

Part 2

Primary Objectives:

- To evaluate the ability of PvP001 and PvP002 to degrade gluten in healthy volunteers
- To determine the effect of standard dose proton pump inhibitor (PPI) pretreatment on the ability of PvP001 to degrade gluten in healthy volunteers

Secondary Objectives:

- To evaluate the safety, tolerability, and gluten-degradation ability of the MTD of PvP001 compared to the Maximum Feasible Dose (MFD) of PvP002 in healthy volunteers
- To determine the PK of PvP001 and PvP002 in healthy volunteers
- To evaluate the ability of PvP001 300 mg and PvP001 600 mg to degrade 1 g of gluten at 20, 35, and 65 minutes in healthy volunteers
- To evaluate the ability of PvP001 900 mg to degrade 6 g of gluten at 20, 35, and 65 minutes in healthy volunteers

Part 3

Primary Objectives:

- To evaluate the ability of PvP003 to degrade gluten in healthy volunteers

Secondary Objectives:

- To evaluate the ability of single doses of PvP003 600 mg with and without pretreatment buffer solution and PvP003 150 mg without pretreatment buffer solution to degrade 1 g of gluten at 35 and 65 minutes in healthy volunteers when administered before a standardized gluten-containing study meal
- To evaluate the ability of single doses of PvP003 600 mg without pretreatment buffer solution to degrade 1 g of gluten at 35 and 65 minutes in healthy volunteers when administered between two portions of a standardized gluten-containing study meal
- To evaluate the ability of single doses of PvP003 600 mg without pretreatment buffer solution to degrade 1 g of gluten at 65 minutes in healthy volunteers when administered before a standardized gluten-free study meal followed by a standardized gluten-containing study meal
- To determine the safety and tolerability of single doses of PvP003 150 mg and 600 mg in healthy volunteers
- To determine the PK of single doses of PvP003 150 mg and 600 mg in healthy volunteers
- To measure the development of anti-drug antibodies (ADA) after administration of single doses of PvP003 150 mg and 600 mg in healthy volunteers

Part 4

Primary Objectives:

- To determine the safety and tolerability of multiple doses of PvP003 600 mg in healthy volunteers

Secondary Objectives:

- To determine the PK of multiple doses of PvP003 600 mg in healthy volunteers
- To measure the development of ADA after administration of multiple doses of PvP003 600 mg in healthy volunteers

Endpoints:

Part 1

Primary Endpoints:

- Type, frequency, severity, and relatedness of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), laboratory abnormalities, changes in electrocardiograms (ECGs), changes in vital signs, and changes in physical examination findings with PvP001
- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP002

Secondary Endpoints:

- Plasma concentrations and calculated PK parameters of PvP001
- Development of anti-drug antibodies (ADA) to PvP001
- Plasma concentrations and calculated PK parameters of PvP002
- Development of ADA to PvP002
- MTD of PvP001 for use in Part 2 of the study

Part 2

Primary Endpoints:

- Gluten degradation by PvP001 in a standardized 3 g gluten-containing study meal
- Gluten degradation by PvP002 in a standardized 3 g gluten-containing study meal
- Gluten degradation by PvP001 in a standardized 3 g gluten-containing study meal following 7 days of standard dose PPI treatment
- Gluten degradation by PvP001 300 mg and PvP001 600 mg in a standardized 1 g gluten-containing study meal at 20, 35, and 65 minutes
- Gluten degradation by PvP001 900 mg in a standardized 6 g gluten-containing study meal at 20, 35, and 65 minutes

Secondary Endpoints:

- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP001
- Plasma concentrations and calculated PK parameters of PvP001
- Development of ADA to PvP001
- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP002
- Plasma concentrations and calculated PK parameters of PvP002
- Development of ADA to PvP002

Part 3

Primary Endpoint:

- Gluten degradation by PvP003 150 mg and 600 mg in a standardized 1 g gluten-containing study meal

Secondary Endpoints:

- Gluten degradation at 35 and 65 minutes by a single dose of PvP003 600 mg with and without pretreatment buffer solution and PvP003 150 mg without pretreatment buffer solution administered before a standardized 1 g gluten-containing study meal
- Gluten degradation at 35 and 65 minutes by a single dose of PvP003 600 mg without

pretreatment buffer solution administered after an approximately 50 mL portion of a standardized 1 g gluten-containing study meal

- Gluten degradation at 65 minutes by a single dose PvP003 600 mg without pretreatment buffer solution administered before a standardized gluten-free study meal followed approximately 30 minutes later by a standardized 1 g gluten-containing study meal
- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP003 150 mg and 600 mg after a single dose
- Plasma concentrations and calculated PK parameters of PvP003 150 mg and 600 mg after a single dose
- Development of ADA to PvP003 150 mg and 600 mg after administration of a single dose

Part 4

Primary Endpoint:

- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP003 600 mg after multiple doses

Secondary Endpoints:

- Plasma concentrations and calculated PK parameters of PvP003 600 mg after multiple doses
- Development of ADA to PvP003 600 mg after administration of multiple doses

Study Design:

This study has four parts. Each part of the study begins with a Screening Period of up to 4 weeks to allow for completion of Screening procedures and subject scheduling. Each subject will be screened by means of medical history, medication review, Gastrointestinal Symptoms Questionnaire (GSQ), physical examination, vital signs, weight, height, laboratory tests, and ECG. The GSQ is being used as a separate safety monitoring tool in this study to ensure that all gastrointestinal complaints are reported by the subject.

Following completion of all Screening procedures, eligible subjects will be enrolled in the study. Part 1 of the study in healthy subjects will be completed prior to enrollment of any subject in Part 2 of the study.

A subject enrolled in Part 1 of the study will participate in one of five dose Cohorts. Healthy subjects will participate in Cohort 1A-1, 1B-1, 1C-1, 1D-1, or 1E-1, and patients with CeD will participate in Cohort 1A-2, 1B-2, 1C-2, 1D-2, or 1E-2. Enrollment of healthy subjects in each of the five dose Cohorts will occur sequentially. Enrollment of patients with CeD in each of the five dose Cohorts will occur sequentially, but each of these dose Cohorts will be open to enrollment only after demonstration of the safety and tolerability of the same dose level in healthy subjects.

A healthy subject enrolled in Part 2 of the study will participate in one of three Groups (Group 1 [Cohorts 2A, 2B, and 2C]), Group 2 [Cohorts 2D and 2E]), or Group 3 [Cohorts 2F and 2G, Cohorts 2F and 2H, or Cohorts 2I and 2J]). Each Group 1 and Group 2 subject will be randomized to the treatment order. Each Group 3 subject will be randomized to the gluten amount in the study meal, the PvP001 dose, and the treatment order. Enrollment of subjects in Group 1, Group 2, and Group 3 may occur in parallel.

A healthy subject enrolled in Part 3 of the study will participate in one of five Groups (Group 1 [Cohorts 3A and 3B], Group 2 [Cohorts 3C and 3D], Group 3 [Cohorts 3E and 3F), Group 4 [Cohorts 3G and 3H], and Group 5 [Cohorts 3I and 3J]). Each Group 1, Group 2, Group 3, Group 4, and Group 5 subject will be randomized to the treatment order. Enrollment of subjects in Group 1, Group 2, Group 3, Group 4, and Group 5 will occur sequentially.

A healthy subject enrolled in Part 4 of the study will participate in two Cohorts (Cohort 4A and Cohort 4B). Each Part 4 subject will be randomized to the treatment order. Enrollment of subjects in Part 4 may occur in parallel with enrollment of subjects in Part 3.

Subjects who participate in Part 1 or Part 2 of the study, and who are not ADA positive, may participate in Part 3 or Part 4 of the study. No other subjects may participate in more than one Part/Group of the study.

Part 1

This is a single-blind, placebo-controlled, single ascending dose study of PvP001, followed by administration of a single dose of the MFD of PvP002, in healthy adult subjects and adult patients with well controlled CeD.

A single dose of PvP001 placebo, PvP001 100 mg, PvP001 300 mg, or PvP001 900 mg will be administered in ascending order to healthy subjects in Cohorts 1A-1, 1B-1, 1C-1, and 1D-1, and to patients with CeD in Cohorts 1A-2, 1B-2, 1C-2, and 1D-2, respectively. A single dose of the MFD of PvP002 will then be administered to healthy subjects in Cohort 1E-1 and to patients with CeD in Cohort 1E-2. Each subject will participate in only one of the five dose Cohorts and will be blinded to the PvP001 and PvP002 dose (PvP001 placebo, PvP001 100 mg, PvP001 300 mg, PvP001 900 mg, or MFD of PvP002). The MFD of PvP002 will not exceed the MTD of PvP001.

Part 1

PvP001 (mg)	Healthy Subject Cohort	Number of Healthy Subjects per Cohort	Celiac Disease Patient Cohort	Number of Patients with Celiac Disease per Cohort
0	1A-1	3-6	1A-2	3-6
100	1B-1	3-6	1B-2	3-6
300	1C-1	3-6	1C-2	3-6
900	1D-1	3-6	1D-2	3-6
PvP002 (mg)				
MFD	1E-1	3-6	1E-2	3-6

Enrollment in each of the five dose Cohorts will begin with healthy subjects in Cohort 1A-1 and will proceed sequentially through Cohort 1E-1 according to the dose escalation guidelines below. Dose-limiting toxicity (DLT) will be defined as a study drug-related serious adverse event (SAE) or a study drug-related adverse event (AE) of Grade 2 or higher based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03[1].

- 3 subjects will be treated at the given PvP001 dose level and the safety data through the Safety Follow Up Call will be reviewed
  - If 0 of these 3 subjects experiences DLT, enrollment of subjects at the next higher dose level will begin
  - If 1 of these 3 subjects experiences DLT, 3 additional subjects will be enrolled at this same dose level
    - If 1 of 6 total subjects at this dose level experiences DLT, enrollment of subjects at the next higher dose level will begin
    - If ≥2 of 6 total subjects at this dose level experience DLT, the MTD will have been exceeded
      - If 6 total subjects were not enrolled at the previous dose level, and the previous dose level was 100 mg or 300 mg, 3 additional subjects will be enrolled at the previous dose level to demonstrate DLT in <2 of 6 subjects and establish this as the MTD of PvP001 to be used in Part 2
- 3 subjects will be treated with the MFD of PvP002 and the safety data through the Safety Follow Up Call will be reviewed
  - If 0 of these 3 subjects experiences DLT, the MFD of PvP002 will be used in Part 2
  - If 1 of these 3 subjects experiences DLT, 3 additional subjects will be treated with the MFD of PvP002
    - If 1 of 6 total subjects treated with the MFD of PvP002 experiences DLT, the MFD of PvP002 will be used in Part 2
    - If ≥2 of 6 total subjects treated with the MFD of PvP002 experience DLT, the MFD of PvP002 will not be used in Part 2

[1] Common Terminology Criteria for Adverse Events Version 4.03. Bethesda (MD): National Cancer Institute (US); 2010 Jun. (NIH publication; no. 10-5410). Available from: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Once a given PvP001 dose level or the MFD of PvP002 is deemed safe in healthy subjects based on these guidelines, enrollment of patients with CeD will begin at this dose level and will proceed according to the same dose escalation guidelines. This may occur simultaneously with enrollment of healthy subjects in the next higher PvP001 dose Cohort or in the MFD of PvP002 Cohort. Patients with CeD enrolled in Part 1 of the study will only be administered dose levels of PvP001 or PvP002 that have previously been deemed safe and well tolerated in healthy subjects.

Each subject will report to the Clinical Research Center the afternoon prior to the Cohort Treatment Day (i.e., on Cohort Treatment Day -1). The subject will eat a gluten-free dinner at the Clinical Research Center and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours). Pretreatment buffer solution (to raise the fasting gastric pH to a level above which the enzyme in PvP001 and PvP002 is stable), followed by study drug, will be administered orally immediately prior to beginning the ingestion of a standardized gluten-free study meal. The entire study meal will be ingested within 10 minutes of study drug administration.

A blood sample will be obtained before pretreatment buffer solution administration, at several time points for approximately 480 minutes (8 hours) after study drug administration on the Cohort Treatment Day, and at the 24-Hour Safety Assessment approximately 24 hours after study drug administration to evaluate systemic exposure to PvP001 and PvP002.

Ice chips (a maximum of 240 mL up to every hour) may be ingested beginning one hour after study drug administration and continuing until ad libitum ingestion of food and liquids begins. Ingestion of food and liquids (normal diet in a healthy subject and gluten-free diet [GFD] in a patient with CeD) ad libitum may begin approximately 185 minutes after study drug administration, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. The subject will begin an overnight fast (nothing by mouth except water for at least 12 hours) prior to the 24-Hour Safety Assessment.

The 24-Hour Safety Assessment will occur for each subject approximately 24 hours after study drug administration.

Each subject will be discharged from the Clinical Research Center following completion of the 24-Hour Safety Assessment, and when the Investigator determines that the subject is in stable condition.

A Safety Follow Up Call will occur for each subject 5 ± 2 days after the 24-Hour Safety Assessment. At the discretion of the Investigator, the subject will return to the Clinical Research Center for a safety follow up visit and/or a safety follow up procedure(s) (e.g., clinical laboratory tests).

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day to test for ADA to PvP001 and PvP002. In a subject who develops ADA, the ADA level will be monitored until it returns to the pre-dose baseline.

Part 2

This is a single-blind, placebo-controlled, single dose study of PvP001 and PvP002 using gastric sample aspiration to evaluate gluten degradation in healthy adult subjects under the following conditions: (a) In Group 1, administration of PvP001 placebo, the MTD of PvP001, and the MTD of PvP001 following 7 days of PPI treatment, before a standardized 3 g gluten-containing study meal, (b) In Group 2, administration of the PvP002 comparator (sterile water) and the MFD of PvP002, before a standardized 3 g gluten-containing study meal, and (c) In Group 3, administration

of PvP001 placebo, PvP001 300 mg, and PvP001 600 mg before a standardized 1 g gluten-containing study meal, and administration of PvP001 placebo and PvP001 900 mg before a standardized 6 g gluten-containing study meal. (Note: The MTD of PvP001 in healthy volunteers has been determined to be 900 mg and has been administered to Group 1 healthy volunteers before a 3 g gluten-containing study meal. This dose of PvP001 and placebo will be administered before a higher [6 g] gluten-containing meal, and two lower doses [300 mg and 600 mg] of PvP001 and placebo will be administered before a lower [1 g] gluten-containing meal, in Group 3 healthy volunteers.)

Twelve subjects will participate in Group 1 and will receive PvP001 placebo, the MTD of PvP001, and the MTD of PvP001 following 7 days of treatment with a standard dose of a PPI; each of these 12 subjects will receive all three treatments, but will be randomized to the treatment order. Group 1 subjects will be blinded to the PvP001 dose (placebo or the MTD).

Ten unique subjects will participate in Group 2 and will receive the PvP002 comparator (sterile water) and the MFD of PvP002; each of these 10 subjects will receive both treatments, but will be randomized to the treatment order. Group 2 subjects will be blinded to which of the two treatments is active study drug.

Twenty-four unique subjects will participate in Group 3. Each subject will receive two treatments, but will be randomized to the treatment order. Eight subjects will be randomized to receive a 1 g gluten-containing study meal; the two treatments will be PvP001 placebo and PvP001 300 mg. Eight subjects will be randomized to receive a 1 g gluten-containing study meal; the two treatments will be PvP001 placebo and PvP001 600 mg. Eight subjects will be randomized to receive a 6 g gluten-containing study meal; the two treatments will be PvP001 placebo and PvP001 900 mg. Group 3 subjects will be blinded to the PvP001 dose (placebo, 300 mg, 600 mg, or 900 mg) and to the amount of gluten in the study meal.

A subject may not participate in more than one Group. Enrollment of subjects in Group 1, Group 2, and Group 3 may occur in parallel.

Part 2

Group	Cohort	PvP001 (mg)	Number of Healthy Subjects per Group
1[a]	2A	0	12
	2B	MTD	
	2C	MTD with PPI	
		PvP002 (mg)	
2[a]	2D	0	10
	2E	MFD	
		PvP001 (mg)	
3[b]	2F	0	24
	2G	300	
	2H	600	
	2I	0	
	2J	900	

MFD = maximum feasible dose; MTD = maximum tolerated dose; PPI = proton pump inhibitor

[a] Group 1 and Group 2 subjects will ingest a standardized 3 g gluten-containing study meal.

[b] Group 3 Cohort 2F, 2G, and 2H subjects will ingest a standardized 1 g gluten-containing study meal; Group 3 Cohort 2I and 2J will ingest a standardized 6 g gluten-containing study meal.

A subject enrolled in Group 1, Group 2, or Group 3 will participate in each Cohort Treatment Day sequentially, in the treatment order to which the subject was randomized, unless one of the individual subject stopping criteria below is met. In this case, the subject will be withdrawn from the study.

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

Each subject will report to the Clinical Research Center the afternoon prior to each Cohort Treatment Day (i.e., on Cohort Treatment Day -1). The subject will eat a gluten-free dinner at the Clinical Research Center and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

On each Cohort Treatment Day, a single-lumen catheter (nasogastric [NG] tube) will be introduced into the stomach. (Note: An orogastric [OG] tube may be used if the Investigator determines that it is preferable for a given subject.) Auscultation and gastric pH testing will be used to confirm tube placement.

Pretreatment buffer solution, followed by study drug, will be administered orally immediately prior to beginning the ingestion of a standardized 3 g gluten-containing study meal (Group 1 and Group 2) or a standardized 1 g gluten-containing or 6 g gluten-containing study meal (Group 3). The entire study meal will be ingested within 10 minutes of study drug administration.

The use of the NG tube will facilitate aspiration of gastric contents to measure the concentration of gluten (i.e., to assess gluten degradation). A gastric sample (approximately 5 mL) will be obtained via the NG tube before pretreatment buffer solution administration. A gastric sample (entire gastric content) will be obtained via the NG tube 35 minutes after study drug administration in a Group 1 and Group 2 subject. A gastric sample (approximately 5 mL) will be obtained via the NG tube 20 and 35 minutes after study drug administration, and a gastric sample (entire gastric content) will be obtained via the NG tube 65 minutes after study drug administration, in a Group 3 subject. Gastric pH testing will also be performed on these samples; the pH of the gastric sample obtained before pretreatment buffer solution administration will be used to confirm that the NG tube is in the stomach and will serve as the pretreatment pH measurement. The aspirated volume of the entire gastric content sample obtained 35 minutes after study drug administration in a Group 1 and Group 2 subject and 65 minutes after study drug administration in a Group 3 subject will be measured before a portion is removed for pH testing and gluten quantification.

A blood sample will be obtained before pretreatment buffer solution administration and at several time points for approximately 480 minutes (8 hours) after study drug administration on each Cohort Treatment Day to evaluate systemic exposure to PvP001 and PvP002.

A urine sample will be obtained before and approximately 240 minutes after study drug administration on each Cohort Treatment Day in a Group 3 subject to test for gluten immunogenic peptides, provided the subject consents to this.

Ingestion of food and liquids (normal diet) ad libitum may begin approximately 185 minutes after study drug administration in a Group 1 and Group 2 subject and ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade,

100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration in a Group 3 subject, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides) in a Group 3 subject. The NG tube will have been removed prior to the ingestion of food and liquids (normal diet) ad libitum in a Group 1 and Group 2 subject and prior to the ingestion of plain gluten-free food and liquids in a Group 3 subject.

Each subject will be discharged from the Clinical Research Center following completion of all study procedures on each Cohort Treatment Day, and when the Investigator determines that the subject is in stable condition. Each subject will have a washout period of 7 ± 1 days (Group 1 and Group 2) or 3 ± 1 days (Group 3) between Cohort Treatment Days.

A Safety Visit will occur for each Part 2 subject 5 ± 2 days after the final Cohort Treatment Day, or 5 ± 2 days after the subject's last Cohort Treatment Day for a subject who withdraws early from the study.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day to test for ADA to PvP001 and PvP002. In a subject who develops ADA, the ADA level will be monitored until it returns to the pre-dose baseline.

Part 3

This is a single-blind, placebo-controlled, single dose study of PvP003, a tablet formulation, using gastric sample aspiration to evaluate gluten degradation in healthy adult subjects under the following conditions: (a) In Group 1, administration of PvP003 placebo and PvP003 600 mg with pretreatment buffer solution before a standardized 1 g gluten-containing study meal, (b) In Group 2, administration of PvP003 placebo and PvP003 600 mg without pretreatment buffer solution before a standardized 1 g gluten-containing study meal, (c) In Group 3, administration of PvP003 placebo and PvP003 600 mg without pretreatment buffer solution after an approximately 50 mL portion of a standardized 1 g gluten-containing study meal, (d) In Group 4, administration of PvP003 placebo and PvP003 600 mg without pretreatment buffer solution before a standardized gluten-free study meal followed approximately 30 minutes later by a standardized 1 g gluten-containing study meal, and (e) In Group 5, administration of PvP003 placebo and PvP003 150 mg without pretreatment buffer solution before a standardized 1 g gluten-containing study meal. Data from both the 600 mg dose and the 150 mg split tablet dose will provide data on activity across the expected clinically relevant dose range to inform future formulation development and doses for inclusion in planned clinical trials.

Thirty-six unique subjects (6 subjects in each of the following four Groups: Group 1, Group 2, Group 3, and Group 4, and 12 subjects in Group 5) will participate in Part 3 and will receive PvP003 placebo and PvP003 150 mg or 600 mg as noted below; each of these 36 subjects will receive both treatments, but will be randomized to the treatment order. Part 3 subjects will be blinded to which of the two treatments is active study drug.

A subject may not participate in more than one Group. Enrollment of subjects in Group 1, Group 2, Group 3, Group 4, and Group 5 will occur sequentially.

Part 3

Group	Cohort	PvP003 (mg)	Pretreatment Buffer Solution Administered	Number of Healthy Subjects per Group
1[a]	3A	0	Yes	6
	3B	600	Yes	
2[a]	3C	0	No	6
	3D	600	No	
3[a]	3E	0	No	6
	3F	600	No	
4[b]	3G	0	No	6
	3H	600	No	
5[a]	3I	0	No	12
	3J	150	No	

[a] Group 1, Group 2, Group 3, and Group 5 subjects will ingest a standardized 1 g gluten-containing study meal.
[b] Group 4 subjects will ingest a standardized gluten-free study meal followed by a standardized 1 g gluten-containing study meal.

A subject enrolled in Group 1, Group 2, Group 3, Group 4, or Group 5 will participate in each Cohort Treatment Day sequentially, in the treatment order to which the subject was randomized, unless one of the individual subjects meet the stopping criteria below. In this case, the subject will be withdrawn from the study.

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

Each subject will report to the Clinical Research Center the afternoon prior to each Cohort Treatment Day (i.e., on Cohort Treatment Day -1). The subject will eat a gluten-free dinner at the Clinical Research Center and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

On each Cohort Treatment Day, a single-lumen catheter (nasogastric [NG] tube) will be introduced into the stomach. (Note: An OG tube may be used if the Investigator determines that it is preferable for a given subject.) Auscultation and gastric pH testing will be used to confirm tube placement.

Group 1

Pretreatment buffer solution, followed by study drug, will be administered orally immediately prior to beginning the ingestion of a standardized 1 g gluten-containing study meal. The entire study meal will be ingested within 10 minutes of study drug administration.

Group 2 and Group 5

Study drug will be administered orally immediately prior to beginning the ingestion of a standardized 1 g gluten-containing study meal. The entire study meal will be ingested within 10 minutes of study drug administration. No pretreatment buffer solution will be administered.

Group 3

An approximately 50 mL portion of a standardized 1 g gluten-containing study meal will be ingested within 5 minutes. Study drug will be administered orally immediately after completing the ingestion of the approximately 50 mL portion of the study meal (this is approximately one sixth of the entire study meal). The remaining portion of the standardized 1 g gluten-containing study meal will begin to be ingested immediately after study drug administration; this remaining portion of the study meal will be ingested within 10 minutes of study drug administration. No pretreatment buffer solution will be administered.

Group 4

Study drug will be administered orally immediately prior to beginning the ingestion of a standardized gluten-free study meal. The entire gluten-free study meal will be ingested within 10 minutes of study drug administration. A standardized 1 g gluten-containing study meal will begin to be ingested 30 minutes after study drug administration. The entire gluten-containing study meal will be ingested within 10 minutes. No pretreatment buffer solution will be administered.

Group 1, Group 2, Group 3, Group 4, and Group 5

The use of the NG tube will facilitate aspiration of gastric contents to measure the concentration of gluten (i.e., to assess gluten degradation). A gastric sample (approximately 5 mL) will be obtained via the NG tube before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3). A gastric sample (approximately 15 mL) will be obtained via the NG tube 35 minutes after study drug administration in a Group 1, Group 2, Group 3, and Group 5 subject. A gastric sample (entire gastric content) will be obtained 65 minutes after study drug administration in a Group 1, Group 2, Group 3, Group 4, and Group 5 subject. Gastric pH testing will also be performed on these samples; the pH of the gastric sample obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4 and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3) will be used to confirm that the NG tube is in the stomach and will serve as the pretreatment pH measurement. The aspirated volume of the approximately 15 mL gastric sample obtained 35 minutes after study drug administration in a Group 1, Group 2, Group 3, and Group 5 subject and the entire gastric content sample obtained 65 minutes after study drug administration in a Group 1, Group 2, Group 3, Group 4, and Group 5 subject will be measured before a portion is removed for pH testing and gluten quantification.

A blood sample will be obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3), and at several time points for approximately 480 minutes (8 hours) after study drug administration on each Cohort Treatment Day to evaluate systemic exposure to PvP003.

A urine sample will be obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3), and approximately 240 minutes after study drug administration on each Cohort Treatment Day to test for gluten immunogenic peptides, provided the subject consents to this.

Ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides). The NG tube will have been removed prior to the ingestion of plain gluten-free food and liquids.

Each subject will be discharged from the Clinical Research Center following completion of all study procedures on each Cohort Treatment Day, and when the Investigator determines that the subject is in stable condition. Each subject will have a washout period of 3 ± 1 days between Cohort Treatment Days.

A Safety Visit will occur 5 ± 2 days after the final Cohort Treatment Day, or 5 ± 2 days after the subject's last Cohort Treatment Day for a subject who withdraws early from the study.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day to test for ADA to PvP003. In a subject who develops ADA, the ADA level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first.

Part 4

This is a single-blind, placebo-controlled, multiple dose study of PvP003, a tablet formulation, in healthy adult subjects to evaluate safety following repeated administrations.

Six unique subjects will participate in Part 4 and will receive PvP003 placebo and PvP003 600 mg; each of these 6 subjects will receive both treatments three times a day (TID) for 5 days, but will be randomized to the treatment order. Part 4 subjects will be blinded to which of the two treatments is active study drug. No pretreatment buffer solution will be administered.

Enrollment of subjects in Part 4 may occur in parallel with enrollment of subjects in Part 3.

Part 4

Cohort	PvP003 (mg) TID X 5 Days	Number of Healthy Subjects
4A	0	6
4B	600	

TID = three times a day

A subject enrolled in Part 4 will participate in each 5-day Cohort Treatment Period sequentially, in the treatment order to which the subject was randomized, unless one of the individual subjects meets the stopping criteria below. In this case, the subject will be withdrawn from the study.

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

Each subject will report to the Clinical Research Center the afternoon prior to Day 1 and Day 5 of each Cohort Treatment Period. On Day 1 and Day 5 of each Cohort Treatment Period, the first

daily dose of study drug (PvP003 placebo or PvP003) will be administered orally by study personnel immediately prior to the subject beginning the ingestion of a regular meal (i.e., breakfast).

A blood sample will be obtained before and at several time points for approximately 240 minutes (4 hours) after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period to evaluate systemic exposure to PvP003.

A urine sample will be obtained before the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period to test for gluten immunogenic peptides, provided the subject consents to this.

Ingestion of any type of snack food and liquids may begin approximately 135 minutes after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of a regular meal (i.e., lunch) may begin approximately 255 minutes after administration of the first daily dose of study drug (i.e., after completion of the 240-minute post-dose PK sampling and clinical laboratory tests [Day 1], or after completion of the 240-minute post-dose PK sampling [Day 5], and immediately after administration of the second daily dose of study drug) on Day 1 and Day 5 of each Cohort Treatment Period.

Each subject will be discharged from the Clinical Research Center following completion of all study procedures on Day 1 and Day 5 of each Cohort Treatment Period, and when the Investigator determines that the subject is in stable condition. After discharge on Day 1 of each Cohort Treatment Period (i.e., beginning with the third daily dose of study drug on Day 1), study drug will be self-administered TID before regular meals (i.e., breakfast, lunch, and dinner) until the subject is admitted to the Clinical Research Center on Day 4 of each Cohort Treatment Period (i.e., after the second daily dose of study drug on Day 4). Each subject will have a washout period of 3 ± 1 days between the two Cohort Treatment Periods (i.e., between Day 5 of the first Cohort Treatment Period and Day 1 of the second Cohort Treatment Period).

A Safety Visit will occur 5 ± 2 days after Day 5 of the second Cohort Treatment Period, or 5 ± 2 days after the subject's last dose of study drug for a subject who withdraws early from the study.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after Day 5 of the second Cohort Treatment Period to test for ADA to PvP003. In a subject who develops ADA, the ADA level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first.

Number of Planned Subjects:

Part 1

Approximately 15-30 eligible healthy subjects and 15-30 eligible patients with CeD will participate in Part 1 of the study (i.e., approximately 3-6 healthy subjects will participate in each of five dose Cohorts and approximately 3-6 patients with CeD will participate in each of five dose Cohorts).

Part 2

Approximately 46 eligible subjects will participate in Part 2 of the study (i.e., approximately 12 subjects will participate in Group 1, approximately 10 subjects will participate in Group 2, and approximately 24 subjects will participate in Group 3).

Part 3

Approximately 36 eligible healthy subjects will participate in Part 3 of the study (i.e., approximately 6 subjects each in Group 1, Group 2, Group 3, and Group 4, and approximately 12 subjects in Group 5).

Part 4

Approximately 6 eligible healthy subjects will participate in Part 4 of the study.

Study Population:

The study population will consist of healthy adults 18-59 years of age, inclusive, and adults with CeD 18-64 years of age, inclusive. Study entry criteria will be men or women with no significant medical disease (i.e., healthy volunteers in Part 1, Part 2, Part 3, and Part 4) or with well controlled CeD (i.e., patients with CeD in Part 1).

Inclusion Criteria:

Part 1, Part 2, Part 3, and Part 4

1. Male or female age 18- 59 years, inclusive, for healthy volunteers (Part 1, Part 2, Part 3, and Part 4); male or female age 18-64 years, inclusive, for patients with CeD (Part 1)
2. Body mass index <35 kg/m^2
3. Absence of clinically relevant gastrointestinal symptoms and signs as indicated by medical history, GSQ, and physical examination at Screening; medical history review/AE recording on Cohort Treatment Day -1, and medical history review/AE recording, GSQ, and physical examination at the beginning of the Cohort Treatment Day, in a Part 1, Part 2, and Part 3 subject; and medical history review/AE recording on Day -1 and Day 4, and medical history review/AE recording, GSQ, and physical examination at the beginning of Day 1, of the Cohort Treatment Period in a Part 4 subject
4. Able to abstain from alcohol for 72 hours prior to the Screening Visit; for 72 hours prior to and after the Cohort Treatment Day (Part 1, Part 2, and Part 3); for 72 hours prior to the Safety Visit (Part 2 and Part 3); and for 72 hours prior to Day 1 of the first Cohort Treatment Period through the Safety Visit (Part 4)
5. A female subject must have a negative pregnancy test at Screening and on Cohort Treatment Day -1 (Part 1, Part 2, and Part 3) or a negative pregnancy test at Screening and on Day -1 of each Cohort Treatment Period (Part 4), and must agree to continue acceptable birth control measures (e.g., abstinence, a stable hormonal contraceptive, double-barrier method, or vasectomy in partner) from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
6. A male subject must agree to continue acceptable birth control measures (e.g., abstinence, latex condom, or vasectomy), or must have a female partner who will continue acceptable birth control measures (e.g., abstinence, a stable hormonal contraceptive, or double-barrier method), from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
7. Able to read and understand English
8. Able to provide written informed consent

Additional Inclusion Criteria for Part 1, Part 2, Part 3, and Part 4 Healthy Adult Volunteers

9. No current, recent (within 7 days prior to the Screening Visit), or planned (from the Screening Visit through the Safety Follow Up Call [Part 1] or Safety Visit [Part 2, Part 3, and Part 4]) use of over-the-counter or prescription medication via any route of administration. This includes, but is not limited to, aspirin and other nonsteroidal anti-inflammatory drugs (which may affect gastrointestinal permeability), gastric acid suppressive medications, vitamins, minerals, and herbal products. Occasional, as needed use of an over-the-counter medication during this time may be acceptable, provided it is approved by the Investigator and Medical Monitor. The exceptions are a hormonal contraceptive for birth control, provided it has been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit; the per protocol use of topical lidocaine, Miralax, and ondansetron on the Cohort Treatment Days (Part 2 and Part 3); and the per protocol use of Nexium before the Cohort 2C Treatment Day (Part 2 Group 1).
10. No significant medical disease, clinical laboratory evidence of significant medical disease, or significant ECG abnormality per the Investigator's assessment
11. No history of upper or lower gastrointestinal tract disease, disorder, or symptoms; this includes, but is not limited to, gastroesophageal reflux disease, esophageal disease, swallowing disorder, ulcer, abnormal gastric emptying, *Helicobacter pylori* infection, gastrointestinal surgery, irritable bowel syndrome, or CeD
12. No history of intolerance, hypersensitivity, or idiosyncratic reaction to gluten or to any food or food ingredient (including a carbohydrate [e.g., lactose], polyol, additive, or preservative), including a food or food ingredient in the study meal
13. Able to maintain a GFD for 24 hours prior to the Cohort Treatment Day (Part 1, Part 2, and Part 3), or usually ingests meals TID (i.e., breakfast, lunch, and dinner) and is able to continue doing so during each Cohort Treatment Period (Part 4)

Additional Inclusion Criteria for Part 1 Patients with Celiac Disease

14. Documented history of CeD, defined as a history (at the time of diagnosis) of duodenal biopsy findings consistent with active CeD per the patient's medical chart note or pathology report, or of serum tissue transglutaminase immunoglobulin A (tTG IgA) antibodies, deamidated gliadin peptide immunoglobulin A or immunoglobulin G (DGP IgA or DGP IgG) antibodies, or endomysial immunoglobulin A or immunoglobulin G (EMA IgA or EMA IgG) antibodies ≥5 times the upper limit of normal per the patient's medical chart note or laboratory report
15. CeD is well controlled, defined as compliance with a GFD and resolution of chronic symptoms for ≥6 months prior to the Screening Visit; occasional accidental gluten exposure, if it occurred during the 6 months prior to the Screening Visit, should not have resulted in severe symptoms or symptoms lasting >48 hours
16. No history of severe CeD symptoms, defined as symptoms resulting in the inability to perform usual daily activities with gluten exposure, severe gluten-related neurologic symptoms (e.g., ataxia, peripheral neuropathy), or significant gastrointestinal or systemic complications of CeD
17. Serum tTG IgA antibodies ≤1.5 times the upper limit of normal and a normal total IgA at Screening
18. Asthma, allergic rhinitis, or hypothyroidism, if present, must be well controlled and stable for ≥3 months prior to the Screening Visit

19. No other significant medical disease, clinical laboratory evidence of other significant medical disease, or significant ECG abnormality per the Investigator's assessment
20. No current, recent (within 7 days prior to the Screening Visit), or planned (from the Screening Visit through the Safety Follow Up Call) use of aspirin and other nonsteroidal anti-inflammatory drugs (which may affect gastrointestinal permeability), proton pump inhibitors, and herbal products. Occasional, as needed use of an over-the-counter medication during this time may be acceptable, provided it is approved by the Investigator and Medical Monitor. Other acceptable medications are a hormonal contraceptive for birth control, inhaled medication for asthma, oral and intranasal medication for allergic rhinitis, thyroid hormone for hypothyroidism, and other medication that the Investigator and Medical Monitor determine will not compromise the safety of the subject or interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments), provided they have been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.
21. No current active irritable bowel syndrome, no history of abnormal gastric emptying, and, based on the Investigator's assessment, no history of other significant upper or lower gastrointestinal tract disease, disorder, symptoms, or surgery. Current gastroesophageal reflux symptoms or disease which is being treated regularly with an H_2-receptor antagonist or an antacid at the same dose and frequency for ≥1 month prior to the Screening Visit, and which is stable, defined as no symptoms for ≥1 month prior to the Screening Visit, may be acceptable, provided this is approved by the Investigator and will not compromise the safety of the subject or interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments), and the medication can be discontinued 48 hours prior to the Cohort Treatment Day through the 24-Hour Safety Assessment with no expected symptoms, compromise of subject safety, or interference with or complication of study procedures or assessments (including gastrointestinal symptom or sign assessments) during this period of discontinuation.
22. No history of intolerance, hypersensitivity, or idiosyncratic reaction to any other food or food ingredient (including a carbohydrate [e.g., lactose], polyol, additive, or preservative), including a food or food ingredient in the study meal
23. Able to continue a GFD from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit

Exclusion Criteria:

Part 1, Part 2, Part 3, and Part 4

1. Any condition or abnormality (including clinical laboratory, ECG, physical examination, or vital sign abnormalities), current or past, that, in the opinion of the Investigator or Medical Monitor, would compromise the safety of the subject, or would interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments). Such conditions include or may include psychiatric, neurologic/neuromuscular, developmental, cardiovascular, renal, immunologic (including autoimmune), infectious, hematologic (including clotting or bleeding disorder), metabolic, otolaryngologic, or pulmonary disease or disorder. These and any other significant medical history should be discussed with the Medical Monitor prior to subject enrollment.
2. Current symptoms or signs of acute illness

3. Chronic viral infection or immunodeficiency condition
4. Any female who is pregnant, planning to become pregnant during the study, or breast-feeding; any male who is planning to father a child during the study
5. History of intolerance, hypersensitivity, or idiosyncratic reaction to any of the ingredients in PvP001, PvP002, PvP003, PvP003 placebo, or the CCI retreatment buffer solution
6. History of intolerance, hypersensitivity, or idiosyncratic reaction to an aminoglycoside
7. Receipt (or planned receipt) of an investigational medication within 4 weeks prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
8. Alcohol consumption >5 drinks/week, alcohol consumption within 72 hours prior to any study visit (Part 1, Part 2, and Part 3), alcohol consumption within 72 hours prior to Day 1 of the first Cohort Treatment Period through the Safety Visit (Part 4), or a positive alcohol breathalyzer test at any study visit
9. History of illicit or recreational drug use within the three years prior to the Screening Visit, or a positive urine drug screen at any study visit
10. Positive *Helicobacter pylori* breath test at Screening
11. Use of tobacco or nicotine products, including smoking, smokeless tobacco, e-cigarettes, or nicotine replacement products within 12 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
12. History or high risk of noncompliance with treatment or clinic visits

Additional Exclusion Criteria for Part 2 and Part 3

13. History of intolerance, hypersensitivity, or idiosyncratic reaction to lidocaine (or other ingredients in the topical lidocaine preparation) or other local anesthetics, Nexium (or other ingredients in the capsule) or other PPIs, polyethylene glycol (PEG), or ondansetron (or other ingredients in the injectable ondansetron preparation) or other serotonin 5-HT_3 receptor antagonists
14. For a Part 2 and Part 3 subject in whom an NG tube will be placed, history of upper respiratory tract trauma or surgery, mid-face trauma, or skull base fracture; current or history of septal perforation, ulceration, or erosion, nasal or sinus polyps, sinus disease, or severe nasal bleeding; current septal deviation, nasal obstruction or congestion, or noninfectious rhinitis that, in the opinion of the Investigator or Medical Monitor, would compromise the safety of the subject. (For a Part 2 and Part 3 subject in whom an OG tube will be placed, current or history of oropharyngeal or dental signs, symptoms, or disease that, in the opinion of the Investigator or Medical Monitor, would compromise the safety of the subject, or current loose tooth.)

Study Treatments, Dose, and Mode of Administration:

A pretreatment buffer solution, CCI , will be supplied as a liquid and stored refrigerated prior to use; 50 mL will be administered orally.

PvP001 is a liquid containing the active enzyme, Kuma062, in formulation buffer. PvP001 will be supplied as a frozen liquid and will be thawed prior to administration. It will be diluted with sterile water immediately before oral administration. Four different PvP001 doses will be administered; however, all four doses will be diluted with sterile water to the same total volume (100 mL). The resulting concentrations of PvP001 in 100 mL will be 1 mg/mL for the 100 mg dose, 3 mg/mL for

the 300 mg dose, 6 mg/mL for the 600 mg dose, and 9 mg/mL for the 900 mg dose.

PvP002 is a capsule containing the same active enzyme, Kuma062, in a dry powder formulation. The MFD of PvP002 will be based on the amount of enzyme included in each capsule and the maximum number of capsules that can easily be swallowed by a subject with 100 mL of sterile water. The MFD of PvP002 is expected to be in the range of 300-400 mg (e.g., 3-4 capsules, each containing 100 mg of active enzyme), but will not exceed the MTD of PvP001. PvP002 capsules will be swallowed with 100 mL of sterile water.

PvP003 300 mg is a tablet containing the same active enzyme, CCI [redacted] In subjects receiving PvP003 600 mg, two PvP003 placebo tablets or PvP003 300 mg tablets will be swallowed with 100 mL of sterile water during the subject's admission at the Clinical Research Center or with water (e.g., tap or bottled) in the amount needed outside of the Clinical Research Center. In subjects receiving PvP003 150 mg, one PvP003 placebo tablet or PvP003 300 mg tablet will be cut approximately in half and will be swallowed with 100 mL of sterile water during the subject's admission at the Clinical Research Center. The dose will be confirmed by the weight of the split tablet and must be within 10% of the target weight for half of a tablet. Data from both the 600 mg dose and the 150 mg split tablet dose will provide data on activity across the expected clinically relevant dose range to inform future formulation development and doses for inclusion in planned clinical trials.

In Part 1 and Part 2 (Group 1 and Group 3) of the study, PvP001 placebo will be 100 mL of sterile water administered orally. In Part 2 (Group 2) of the study, the PvP002 comparator will be 100 mL of sterile water administered orally. In Part 3 (Group 1, Group 2, Group 3, Group 4, and Group 5) and Part 4 of the study, PvP003 placebo will be a tablet containing CCI [redacted] administered orally, indistinguishable by taste and appearance (e.g., shape, size, color) from the PvP003 300 mg tablet.

In Part 1 of the study, a standardized blended gluten-free study meal consisting of ice cream, egg whites, orange juice, lime juice, vanilla extract, and gluten-free bread will be prepared and frozen until prior to ingestion, at which time it will be removed from the freezer and partially thawed at room temperature.

In Part 2 of the study, a standardized blended gluten-containing study meal consisting of ice cream, egg whites, orange juice, lime juice, vanilla extract, and whole wheat bread containing 3 g of gluten (Group 1 and Group 2), whole wheat bread containing 1 g of gluten (Group 3 Cohorts 2F, 2G, and 2H), or whole wheat bread containing 3 g of gluten as well as 3 g of gluten powder added to the meal (Group 3 Cohorts 2I and 2J) will be prepared and frozen until prior to ingestion, at which time it will be removed from the freezer and partially thawed at room temperature. One gram of PEG 3350 powder will be added to and blended with the other ingredients at the time the standardized gluten-containing study meal is prepared and will serve as a marker of total gastric volume.

In Part 3 of the study, a standardized blended gluten-containing study meal consisting of ice cream, egg whites, orange juice, lime juice, vanilla extract, and whole wheat bread containing 1 g of gluten (Group 1 Cohorts 3A and 3B, Group 2 Cohorts 3C and 3D, Group 3 Cohorts 3E and 3F, Group 4 Cohorts 3G and 3H, and Group 5 Cohorts 3I and 3J) will be prepared and frozen until prior to ingestion, at which time it will be removed from the freezer and partially thawed at room temperature. One gram of PEG 3350 powder will be added to and blended with the other ingredients at the time the standardized 1 g gluten-containing study meal is prepared and will serve as a marker

of total gastric volume. In Part 3 of the study, a standardized blended gluten-free study meal consisting of ice cream, egg whites, orange juice, lime juice, vanilla extract, and gluten-free bread (Group 4 Cohorts 3G and 3H) will also be prepared and frozen until prior to ingestion, at which time it will be removed from the freezer and partially thawed at room temperature.

In Part 4 of the study, regular meals will be ingested, and no standardized study meal will be administered.

Pretreatment buffer solution will be swallowed immediately prior to study drug administration. Study drug will be swallowed immediately after the pretreatment buffer solution and immediately prior to beginning the ingestion of the study meal. The entire study meal will be ingested within 10 minutes of study drug administration.

Standard dose PPI treatment, defined in this study as Nexium 20 mg once daily, will be administered orally at bedtime for 7 days prior to the Cohort 2C Treatment Day. The final dose (dose 7) of Nexium will be administered to the subject by the Clinical Research Center personnel at bedtime the night before the Cohort 2C Treatment Day (i.e., on Cohort 2C Treatment Day -1).

Duration of Participation:

Each part of the study begins with a Screening Period of up to 4 weeks to allow for completion of Screening procedures and subject scheduling.

Part 1

Each subject will participate in the study for up to approximately 8 weeks, including the Screening Period, Cohort Treatment Day with post-dose 24-Hour Safety Assessment, Safety Follow Up Call 5 ± 2 days after the 24-Hour Safety Assessment, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day.

Part 2

Each subject enrolled in Group 1 will participate in the study for up to approximately 10 weeks, including the Screening Period, three Cohort Treatment Days, washout period of 7 ± 1 days between each of the Cohort Treatment Days, Safety Visit 5 ± 2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Each subject enrolled in Group 2 will participate in the study for up to approximately 9 weeks, including the Screening Period, two Cohort Treatment Days, washout period of 7 ± 1 days between each of the Cohort Treatment Days, Safety Visit 5 ± 2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Each subject enrolled in Group 3 will participate in the study for up to approximately 9 weeks, including the Screening Period, two Cohort Treatment Days, washout period of 3 ± 1 days between each of the Cohort Treatment Days, Safety Visit 5 ± 2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Part 3

Each subject will participate in the study for up to approximately 9 weeks, including the Screening Period, two Cohort Treatment Days, washout period of 3 ±1 days between each of the Cohort

Treatment Days, Safety Visit 5 ±2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Part 4

Each subject will participate in the study for up to approximately 10 weeks, including the Screening Period, two 5-day Cohort Treatment Periods, washout period of 3 ±1 days between the two Cohort Treatment Periods, Safety Visit 5 ±2 days after Day 5 of the second Cohort Treatment Period, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after Day 5 of the second Cohort Treatment Period.

Efficacy Assessments:

In Part 2 of the study, the concentration of immunogenic gluten peptides remaining in the stomach after treatment with study drug and ingestion of a standardized gluten-containing meal will be measured 35 minutes (Group 1 and Group 2) and 20, 35, and 65 minutes (Group 3) after study drug administration using enzyme-linked immunosorbent assays (ELISA) based on the commercially available monoclonal R5 and G12 antibodies that are specific for immunogenic fractions of gluten. CCI [redacted]

In Part 3 of the study, the concentration of immunogenic gluten peptides remaining in the stomach after treatment with study drug and ingestion of a standardized gluten-containing meal will be measured 35 and 65 minutes (Group 1, Group 2, Group 3, and Group 5) and 65 minutes (Group 4) after study drug administration using ELISA based on the commercially available monoclonal R5 and G12 antibodies that are specific for immunogenic fractions of gluten. CCI [redacted]

Gastric samples will be banked for possible future testing for gluten degradation, provided the subject consents to this.

Pharmacokinetic Assessments:

Pharmacokinetic testing will be done to evaluate systemic exposure to PvP001, PvP002, and PvP003.

A blood sample for PK testing will be obtained before pretreatment buffer solution administration and approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration on the Cohort Treatment Day in Part 1 and Part 2 of the study. A blood sample for PK testing will also be obtained at the 24-Hour Safety Assessment, approximately 24 hours after study drug administration in Part 1 of the study.

A blood sample for PK testing will be obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3), and approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration on the Cohort Treatment Day in Part 3 of the study.

A blood sample for PK testing will be obtained before and approximately 15, 30, 45, 60, 120, 180, and 240 minutes after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period in Part 4 of the study.

Testing of these samples for PvP001, PvP002, and PvP003 will be performed using a validated method.

Safety Assessments:

Safety assessments will be conducted throughout the study and will include monitoring of AEs, GSQs, physical examinations, vital signs, weight assessments, clinical laboratory tests (chemistry, hematology, and urinalysis), ADA testing, serum and urine pregnancy tests (in females), and ECGs.

The GSQ will include nine items (abdominal discomfort, abdominal pain, abdominal bloating, constipation, diarrhea, passing gas, belching/burping, nausea, and heartburn), each rated on a five-point Likert scale on which the lowest score, 0, denotes no symptoms and the highest score, 4, denotes the most pronounced symptoms. In Part 1 of the study, each subject will complete the GSQ on the Cohort Treatment Day pre-dose (i.e., before pretreatment buffer solution administration) and post-dose (i.e., after completion of study meal ingestion) to ensure that all gastrointestinal complaints are reported by the subject. In Part 2 and Part 3 of the study, each subject will complete the GSQ on each Cohort Treatment Day pre-dose (i.e., before and after NG tube placement) and post-dose (i.e., after completion of study meal ingestion) to ensure that all gastrointestinal complaints are reported by the subject. In Part 4 of the study, each subject will complete the GSQ on Day 1 and Day 5 of each Cohort Treatment Period pre-dose (i.e. before administration of the first daily dose of study drug) and on Day 1 of each Cohort Treatment Period post-dose (i.e., after completion of breakfast ingestion), as well as every day at bedtime from Day 1 of the first Cohort Treatment Period through the day prior to the Safety Visit, to ensure that all gastrointestinal complaints are reported by the subject.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day (Part 1), after the final Cohort Treatment Day (Part 2 and Part 3), or after Day 5 of the second Cohort Treatment Period (Part 4) to test for ADA to PvP001, PvP002, and PvP003. Testing of samples for ADA will be performed using validated assays. Confirmed positive samples will be further tested for neutralizing activity. In a Part 1 and Part 2 subject who develops ADA, the ADA level will be monitored until it returns to the pre-dose baseline. In a Part 3 and Part 4 subject who develops ADA, the ADA level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first. As appropriate, the potential impact of ADA on safety, efficacy, and PK will be assessed.

Sample Size Justification:

No formal sample size calculations were conducted for Part 1, Part 2, or Part 4 of this study. The sample sizes in Part 1, Part 2, and Part 4 of the study were selected to meet the objectives of the clinical trial (i.e., to assess the safety and PK of PvP001, PvP002, and PvP003 in Part 1, Part 2, and Part 4, as well as the gluten degradation ability of PvP001 and PvP002 in Part 2). In addition, in Part 2 of the study, the number of subjects in Group 1 was selected so that at least two subjects would be randomized to each of the six possible treatment orders and the number of subjects in Group 3 was selected so that at least four subjects would be randomized to each of the six possible gluten amount, PvP001 dose, and treatment order combinations; in Part 4 of the study, the number of subjects was selected so that at least three subjects would be randomized to each of the two possible treatment orders.

Sample size determination and justification were conducted only for Part 3 of this study. As residual gluten <50 mg is regarded as meaningful in reducing gluten-induced symptoms, the sample size calculation for Part 3 of the study is based on the proportion of subjects with <50 mg residual gluten. For pooled Part 3 Group 2 and Part 3 Group 3, and for Part 3 Group 5, with a sample size of 12 (i.e., six subjects in Group 2 and six subjects in Group 3), assuming the true (population)

proportion is 85%, the 80% exact confidence interval (CI) will be (62%, 95%) when the observed rate is 83% (10 out of 12 subjects). Based on the width of this CI, the chosen sample size was considered to provide an acceptable level or precision in the estimation of the primary endpoint.

Statistical Methods and Types of Analyses:

Full details of the statistical analyses will be provided in the Statistical Analysis Plan (SAP).

Part 1, Part 2, Part 3, and Part 4 analyses will be presented separately.

Part 1 analyses will be presented by dosage level of PvP001 and the MFD of PvP002. Healthy subjects and patients with CeD will be presented separately and combined.

Part 2 analyses will be presented by Group and Cohort. Select analyses will also be presented by Cohort order in each Group. Additional analyses for Part 2 Group 3 may be described in the SAP.

Part 3 analyses will be presented by Group and Cohort. Select analyses will also be presented by Cohort order in each Group.

Part 4 analyses will be presented by Cohort. Select analyses will also be presented by Cohort order.

In Part 2, the percent of gluten degraded by PvP001 and PvP002 35 minutes after study drug administration will be calculated for each Group 1 and Group 2 subject for each treatment received, and the percent of gluten degraded by PvP001 20, 35, and 65 minutes after study drug administration will be calculated for each Group 3 subject for each treatment received. In Part 3, the percent of gluten degraded by PvP003 35 and 65 minutes after study drug administration will be calculated for each Group 1, Group 2, Group 3, and Group 5 subject for each treatment received, and the percent of gluten degraded by PvP003 65 minutes after study drug administration will be calculated for each Group 4 subject for each treatment received. The gluten amount recovered and the percent of gluten degraded at the scheduled time points after study drug administration will be summarized using descriptive statistics. In addition, the amount of gluten recovered in the subject's stomach after active treatment relative to the amount of gluten recovered in the same subject's stomach after placebo (comparator) treatment will be reported according to the formula utilized by Siegel 2012: percent of gluten degraded = (1 – active/placebo) x 100. For Group 1, this calculation will be done for both active study drug using the MTD (Cohort 2B) and active study drug using the MTD with PPI pretreatment (Cohort 2C).

The count and percentage of subjects reporting TEAEs and TESAEs will be summarized overall, by System Organ Class, by Preferred Term within the System Organ Class, by maximum severity, and by relationship to study drug. In Part 2 and Part 3, AEs and SAEs will also be summarized by relationship to study procedure (i.e., NG tube placement or presence). All other safety parameters, including clinical laboratory values, will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables. Shift tables may be employed to present out-of-range laboratory values and abnormal ECG findings.

Pharmacokinetic analyses to characterize drug exposure will include, at a minimum, determination for each Cohort of maximum plasma concentration, time of maximum plasma concentration, terminal half-life, and areas under the plasma concentration-time curve (AUC) following the dose administration, derived from the plasma concentration-time data. The AUC will be estimated by the linear trapezoidal rule. Actual times at which blood samples are obtained will be used in PK analyses.

An interim analysis will be performed on a subset of subjects in Part 1 and Part 2 of the study.

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LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
ALV003	Designation for mixture of EP-B2 and SC PEP
AN-PEP	*Aspergillus niger* Prolyl Endoprotease
AUC	Area Under the Plasma Concentration-Time Curve
BMI	Body Mass Index
CeD	Celiac Disease
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting Toxicity
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
EP-B2	Endoprotease B, Isoform 2 from Barley
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GFD	Gluten-free Diet
GSQ	Gastrointestinal Symptoms Questionnaire
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgA	Immunoglobulin A
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/Mass Spectrometry
MFD	Maximum Feasible Dose
MTD	Maximum Tolerated Dose
NG	Nasogastric
OG	Orogastric
PEG	Polyethylene Glycol
PK	Pharmacokinetic
PP	Per Protocol
PPI	Proton Pump Inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC PEP	*Sphingomona capsulata* Prolyl Endopeptidase
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TID	Three Times a Day
tTG IgA	Tissue Transglutaminase Immunoglobulin A
US	United States

1 INTRODUCTION AND RATIONALE

1.1 Background

Celiac disease (CeD) is an immunologic disorder in which proximal small intestine inflammation is triggered in genetically susceptible individuals by the ingestion of dietary gluten. Celiac disease is typically associated with a variety of gastrointestinal symptoms, including diarrhea, steatorrhea, bloating, flatulence, abdominal pain, and constipation. Extraintestinal manifestations of the disease include weight loss, decreased body mass index (BMI), lower-than-expected height, abnormal liver function tests (elevated transaminase levels) and other liver disorders, iron deficiency anemia, micronutrient deficiencies, low bone mineral density and increased fracture risk, skin disorders, increased risk of infertility and pregnancy complications in women, increased risk of malignancy (e.g., enteropathy-associated lymphoma), and increased risk of mortality (Rubio-Tapia 2013; Rostom 2006). Quality of life is adversely affected by CeD symptoms (Leffler 2016).

Celiac disease, considered an autoimmune disorder, is common throughout the world and its prevalence has increased over the past several decades; its prevalence in the US is approximately 1% (Rostom 2006). Its prevalence is increased in patients with a variety of other autoimmune diseases, and patients with CeD appear to be at increased risk for the development of other autoimmune diseases (Rubio-Tapia 2013; Rostom 2006).

The diagnosis of CeD is usually initially based on signs, symptoms, and serologic testing for CeD-specific antibodies. Serologic tests serve as markers of CeD-specific autoimmunity and are dependent on the ingestion of gluten; when used for diagnostic purposes, such as to confirm a clinical suspicion of CeD, a positive test obtained while a patient is on a gluten-containing diet are supportive of the diagnosis. Confirmation of the diagnosis of CeD requires duodenal mucosal biopsies obtained while a patient is on a gluten-containing diet. The immune response to gluten in CeD leads to chronic inflammation and resultant architectural changes in the intestinal mucosa. Histologic findings include villous atrophy, crypt hyperplasia, and inflammatory cell infiltration (Rubio-Tapia 2013; Rostom 2006).

There are no United States (US) Food and Drug Administration (FDA)-approved medications for CeD. The only recommended treatment at this time is a gluten-free diet (GFD). A strict GFD is effective in most patients, with resolution of gastrointestinal symptoms, intestinal damage, and other disease manifestations, but it must be continued throughout the patient's lifetime. However, some patients have persistent CeD manifestations (symptoms, signs, or typical laboratory abnormalities) despite adherence to a GFD for 6-12 months; this is considered non-responsive CeD and occurs in up to 30% (Rubio-Tapia 2013) of patients. The most common cause of non-responsive CeD is inadvertent gluten ingestion (Rubio-Tapia 2013; Rostom 2006), which leads to ongoing or intermittent symptoms and intestinal inflammation.

Although the term "gluten-free diet" implies the complete absence of gluten in the patient's diet, this is not possible due to the presence of hidden sources of gluten in many commercial foods and the contamination of foods with trace amounts of gluten. According to the Codex

Alimentarius[2] and the Federal Register[3], a food labeled "gluten-free" should have less than 20 parts per million (ppm) of gluten (20 mg of gluten per kilogram of food, or 0.002%). The 2013 FDA recommendation for voluntary use in food labeling was based in part on this being the "lowest level at which analytical methods have been scientifically validated to reliably and consistently detect gluten across a range of food matrices," as well as the expected low likelihood that this level of gluten would cause adverse health effects in most individuals with CeD.

Thus, the term "gluten-free diet" actually indicates that the gluten level in the diet is at levels that are considered to have a low risk of harm. The exact level below which dietary gluten is considered "harmless" is not known and is likely to vary between individuals due to differing levels of sensitivity. According to Leonard 2017, trace amounts of gluten that may be present in foods labeled gluten-free may be as harmful as non-adherence to a GFD. One study evaluating intestinal biopsies in patients with CeD who received 0, 10, or 50 mg of gluten per day for 90 days concluded that the daily gluten amount should be <50 mg (Catassi 2007). A systematic review found that less than 10 mg of gluten per day is unlikely to cause significant histologic abnormalities in most patients with CeD (Akobeng 2008; Rubio-Tapia 2013).

Questionnaire-based studies have highlighted the difficulty with maintaining a strict GFD despite the intention to do so, with frequent accidental (including inadvertent) gluten ingestion (Hall 2013); dissatisfaction with the GFD and interest in novel therapies (Aziz 2011); barriers to maintaining a GFD including restaurant eating and the availability and cost of gluten-free foods (Tennyson 2013); the high treatment burden (Shah 2014) and its negative impact on quality of life (Wolf 2017); and the interest in and need for medication (Aziz 2011; Tennyson 2013).

As noted in the report of the third Gastroenterology Regulatory Endpoints and Advancement of Therapeutics workshop held in 2015 (Leffler 2016), limitations to the adherence to and effectiveness of the GFD include the potential for gluten contamination when dining out and with the use of medications and supplements. Patients who report persistent intestinal or extra-intestinal symptoms despite attempting to adhere to a GFD could especially benefit from non-dietary therapies, according to the report. The workshop report also noted that patients desire non-dietary treatments for CeD and are more interested in therapies that protect against gluten contamination than those that facilitate intentional gluten ingestion. It was concluded that there is a high unmet medical need for therapy beyond the GFD (i.e., pharmacologic interventions). Although there currently is no non-dietary therapy with FDA approval for CeD, pharmacologic treatments for CeD are being evaluated in clinical trials, including supplemental enzyme therapy.

One component of gluten, gliadin, constitutes approximately 50% of the total protein composition of gluten and is rich in the amino acids proline (P) and glutamine (Q). In all individuals, gliadin undergoes only partial digestion by gastric, pancreatic, and intestinal brush border proteases in the upper gastrointestinal tract, as these proteases are unable to cleave the proline- and glutamine-rich regions within gliadin. These incompletely digested peptides enter

[2] Standard for Foods for Special Dietary Use for Persons Intolerant to Gluten, CODEX STAN 118-1979 (2015).
[3] Food and Drug Administration (US). Food Labelling; Gluten-Free Labelling of Foods. Final Rule. Fed Regist. 2013;78(150):47154-79.

the small intestine and, in susceptible individuals, can trigger an immune response (Rostom 2006; Lindfors 2012; Kaukinen 2015; Wolf 2015). Thus, oral enzyme supplementation with glutenases is designed to target and break down ingested proline- and glutamine-rich peptides, before they reach the small intestine, into smaller, non-immunogenic peptides.

To address the unmet need for pharmacologic therapy, a variety of enzymes, including those derived from bacteria, fungi, and germinating cereals, have been studied (Lindfors 2012). In published in vitro studies, in vivo (animal) studies, and early phase clinical trials in healthy adult subjects and adult patients with CeD treated with these glutenases, a mixture of a barley-derived endoprotease (EP-B2) that targets the amino acid glutamine and a bacterium-derived prolyl endopeptidase (SC PEP) that targets the amino acid proline, as well as a fungus (*Aspergillus niger*)-derived prolyl endoprotease (AN-PEP), have been reported to degrade and decrease the immunogenicity of gluten (Siegel 2006; Gass 2007; Mitea 2008; Tye-Din 2010; Siegel 2012; Salden 2015; Janssen 2015). For example, Siegel 2012 reported that ALV003 (a mixture of EP-B2 + SC PEP) 100 mg and 300 mg degraded 75% and 88%, respectively, of 1 g of gluten in a meal containing proteins, fats, and carbohydrates in the stomach of healthy adult subjects and adult patients with CeD in two Phase 1 clinical trials evaluating ALV003 as a potential oral treatment to be used in conjunction with a GFD for CeD. Tye-Din 2010 reported the results of a study in which adult patients with CeD who were following a GFD and were challenged for three days with a single daily dose of 16 mg of gluten that had been pretreated before ingestion with a mixture of EP-B2 and SC PEP, designated ALV003. Gluten-specific peripheral T cell responses were noted in significantly fewer patients in the group challenged with ALV003-pretreated gluten compared to the group challenged with placebo-pretreated gluten, and the mean increases in T cell responses from baseline to day 6 were significant in the group challenged with placebo-pretreated gluten.

Overall, however, in clinical trials of patients with CeD, symptomatic (Tye-Din 2010; Tack 2013; Lahdeaho 2014; Murray 2017; Syage 2017) or histologic (Tack 2013; Lahdeaho 2014; Murray 2017) responses associated with the use of these enzymes have not been consistently seen.

Significant safety issues have not been reported in these clinical trials with EP-B2 + SC PEP (ALV003, latiglutenase) or AN-PEP (Tye-Din 2010; Siegel 2012; Tack 2013; Lahdeaho 2014; Salden 2015; Murray 2017), including in patients with CeD. In the study reported by Siegel 2012, systemic exposure to the two components of ALV003 was low (i.e., EP-B2 was detected in a single sample collected two hours after dosing in a fasting subject who received the highest dose [1800 mg]). Seven of the subjects who received ALV003 in the fasting state developed antibodies to EP-B2, although there were no related clinical symptoms or sequelae (Siegel 2012). AN-PEP has become commercially available in the US as a dietary supplement (Tolerase® G; DSM, The Netherlands) and, as such, does not require FDA approval.

Computational protein design allows for the development of proteins, such as enzymes, that have a specified set of characteristics and thus would be ideally suited for the treatment of a target disease. An enzyme that specifically targets the proline-glutamine (PQ) dipeptide, rather than the single amino acid proline (P) or glutamine (Q), found in the immunogenic gliadin peptides is desirable as a potential treatment for CeD (Gordon 2012). Gordon 2012 reported identification of

a naturally-occurring endopeptidase (kumamolisin-As, designated "Kuma"), active in acidic conditions, from the bacterium *Alicyclobacillus sendaiensis*. These researchers then used computational protein design and recombinant technology to reengineer this enzyme to have and to optimize all the traits that would make it suitable for development as oral enzyme therapy for CeD. *In vitro* studies with a highly active version of the enzyme, which the researchers referred to as KumaMax, indicated that it degraded >95% of an immunogenic (immunodominant) peptide present in α-gliadin within 50 minutes (Gordon 2012).

As discussed by Wolf 2015, the proteolytic activity required of an oral enzyme is high, since accidental ingestion of 1 g of gluten (approximately one-fourth of a slice of bread) would require ≥99% degradation within the stomach in a physiologically relevant time frame to reduce the intragastric residual gluten amount to ≤10 mg, which would likely avoid an immunologic response within the duodenum. Thus, the version of Kuma evaluated in the study published by Gordon 2012 was subsequently computationally redesigned to greatly increase enzymatic activity, which resulted in >99% degradation of immunogenic peptides in in vitro studies (Wolf 2015). In simulated gastric digestion studies, the enzyme degraded >99.97% of 10,000 ppm of gluten, which resulted in a remaining level of gluten well below the 20 ppm threshold for "gluten free" labeling (Wolf 2015).

Millennium Pharmaceuticals, Inc. has conducted an in vivo animal study in which the enzyme was capable of degrading up to >99% of gluten in a rat model of human gastric digestion (Report H005, on file, Millennium Pharmaceuticals, Inc.). Millennium Pharmaceuticals, Inc. has also conducted a variety of other laboratory studies with Kuma, including a subsequent version of the enzyme (Kuma062) that was determined to be an optimal version based on comparisons between it and previous versions and which will be used in the current study. Kuma062 has been shown in vitro to rapidly degrade up to >99% of gluten at doses ranging from 80 mg to 800 mg, including over a wide range of pH levels. It has also been shown in vitro and in simulated gastric digestion studies to degrade gluten more effectively than either AN-PEP or EP-B2 + SC PEP, including in simulated gastric digestion studies with a "real world" meal containing a variety of different protein sources in addition to gluten, as well as carbohydrates and fat (Report H007, on file, Millennium Pharmaceuticals, Inc.).

Thus, Kuma062's ability to rapidly and effectively degrade gluten under gastric conditions is expected to greatly reduce the potential of gluten to stimulate the human immune response and is essential to justify human studies assessing enzyme activity in actual meal digestion scenarios. Importantly, even low levels of intestinal gluten exposure can trigger symptoms and mucosal inflammation in patients with CeD.

Finally, the safety profile of Kuma062 has been established in the clinical and nonclinical studies conducted to date; these studies are discussed in the Investigator's Brochure (IB).

1.2 Study Rationale

The only currently recommended treatment for CeD is strict and lifelong adherence to a GFD. In light of the difficulty of strictly adhering to and maintaining a life-long GFD, the substantial risk and common occurrence of inadvertent gluten exposure, even in individuals attempting to adhere to a GFD, and the incomplete response to a GFD in many patients, which is most commonly due to inadvertent gluten exposure, new therapies for CeD are needed and are desired by patients. As there is no non-dietary therapy with FDA approval for CeD, there is a high unmet need for other treatment, especially a pharmacologic intervention that could be used as an adjunct to a GFD. An oral glutenase appears to be a potential new therapy for CeD.

In particular, given the enzyme's ability to rapidly and effectively degrade gluten in the laboratory studies conducted thus far, as well as its safety profile in clinical and nonclinical studies to date, it is important to continue the development of Kuma062 to determine its potential as a new oral enzyme therapy as an adjunct to a GFD for patients with CeD. Therefore, Phase 1 clinical trials are being conducted to determine the safety and efficacy of Kuma062 in humans.

In the current Phase 1 four-part clinical trial, PvP001 (liquid formulation of Kuma062), PvP002 (capsule formulation of Kuma062), and PvP003 (tablet formulation of Kuma062) will be studied. PvP003, a tablet formulation developed after PvP001 and PvP002 in anticipation of Phase 2 clinical development, is expected to be more tolerant of the acidic environment of the stomach, to have more sustained activity in the stomach, and to have comparable gluten-degrading activity to PvP001 and PvP002. PvP001 and PvP002 have been studied in Phase 1 clinical trials; PvP003 has not been previously studied in humans.

- In the first part (Part 1) of the study, the safety of single doses of PvP001 and PvP002 administered in the presence of a standardized gluten-free study meal will be evaluated in healthy adult subjects and in patients with CeD.
- In the second part (Part 2) of the study, the gluten-degrading activity of single doses of PvP001 and PvP002 in the stomach in the presence of a standardized gluten-containing study meal will be evaluated in healthy adult subjects; the effect of pretreatment with seven days of a standard dose of a proton pump inhibitor (PPI) on the gluten-degrading activity of PvP001 will also be evaluated in this part of the study.
- In the third part (Part 3) of the study, the gluten-degrading activity of single doses of PvP003 in the stomach administered (a) with pretreatment buffer solution CCI [redacted] before a standardized gluten-containing study meal (just as pretreatment buffer solution is being administered with the enzyme in liquid and capsule formulations in Part 2 subjects, it is being administered with the enzyme in tablet formulation in this group of Part 3 subjects), (b) without pretreatment buffer solution before a standardized gluten-containing study meal, (c) during a standardized gluten-containing study meal, and (d) before a standardized gluten-free study meal followed by a standardized gluten-containing study meal will be evaluated in healthy adult subjects; and (e) with a lower dose before a standardized gluten-containing study meal.

- In the fourth part (Part 4) of the study, the safety of multiple doses of PvP003 administered in the presence of regular meals will be evaluated in healthy adult subjects to support a longer duration of treatment with this formulation in Phase 2 clinical development.

Positive results from this study will justify evaluating this enzyme further in patients with CeD in future studies.

1.3 Special Considerations

The effect of pretreatment with seven days of a standard dose of a PPI on the ability of PvP001 to degrade gluten in a standardized study meal in the stomach in healthy adult subjects will be evaluated in Part 2 of the study. Pretreatment with a PPI is not expected to reduce the gluten-degrading activity of PvP001, as Kuma062 maintains enzymatic activity at the gastric pH range expected with use of a PPI (e.g., median 24-hour gastric pH on day 5 of dosing with Nexium 20 mg in patients with gastroesophageal reflux disease was 4.1) (Nexium2016).

2 STUDY OBJECTIVES

Part 1

Primary Objective:

- To determine the safety and tolerability of single doses of PvP001 and PvP002 in healthy volunteers and patients with CeD

Secondary Objectives:

- To determine the pharmacokinetics (PK) of PvP001 and PvP002 in healthy volunteers and patients with CeD
- To determine the maximum tolerated dose (MTD) (100, 300, or 900 mg) of PvP001 in healthy volunteers for use in Part 2

Part 2

Primary Objectives:

- To evaluate the ability of PvP001 and PvP002 to degrade gluten in healthy volunteers
- To determine the effect of standard dose PPI pretreatment on the ability of PvP001 to degrade gluten in healthy volunteers

Secondary Objectives:

- To evaluate the safety, tolerability, and gluten-degradation ability of the MTD of PvP001 compared to the maximum feasible dose (MFD) of PvP002 in healthy volunteers
- To determine the PK of PvP001 and PvP002 in healthy volunteers
- To evaluate the ability of PvP001 300 mg and PvP001 600 mg to degrade 1 g of gluten at 20, 35, and 65 minutes in healthy volunteers
- To evaluate the ability of PvP001 900 mg to degrade 6 g of gluten at 20, 35, and 65 minutes in healthy volunteers

Part 3

Primary Objectives:

- To evaluate the ability of PvP003 to degrade gluten in healthy volunteers

Secondary Objectives:

- To evaluate the ability of single doses of PvP003 600 mg with and without pretreatment buffer solution and PvP003 150 mg without pretreatment buffer solution to degrade 1 g of gluten at 35 and 65 minutes in healthy volunteers when administered before a standardized gluten-containing study meal

- To evaluate the ability of single doses of PvP003 600 mg without pretreatment buffer solution to degrade 1 g of gluten at 35 and 65 minutes in healthy volunteers when administered between two portions of a standardized gluten-containing study meal
- To evaluate the ability of single doses of PvP003 600 mg without pretreatment buffer solution to degrade 1 g of gluten at 65 minutes in healthy volunteers when administered before a standardized gluten-free study meal followed by a standardized gluten-containing study meal
- To determine the safety and tolerability of single doses of PvP003 150 mg and 600 mg in healthy volunteers
- To determine the PK of single doses of PvP003 150 mg and 600 mg in healthy volunteers
- To measure the development of anti-drug antibodies (ADA) after administration of single doses of PvP003 150 mg and 600 mg in healthy volunteers

Part 4

Primary Objectives:

- To determine the safety and tolerability of multiple doses of PvP003 600 mg in healthy volunteers

Secondary Objectives:

- To determine the PK of multiple doses of PvP003 600 mg in healthy volunteers
- To measure the development of ADA after administration of multiple doses of PvP003 600 mg in healthy volunteers

3 STUDY ENDPOINTS

Part 1

Primary Endpoints:

- Type, frequency, severity, and relatedness of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), laboratory abnormalities, changes in electrocardiograms (ECGs), changes in vital signs, and changes in physical examination findings with PvP001
- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP002

Secondary Endpoints:

- Plasma concentrations and calculated PK parameters of PvP001
- Development of ADA to PvP001
- Plasma concentrations and calculated PK parameters of PvP002
- Development of ADA to PvP002
- MTD of PvP001 for use in Part 2 of the study

Part 2

Primary Endpoints:

- Gluten degradation by PvP001 in a standardized 3 g gluten-containing study meal
- Gluten degradation by PvP002 in a standardized 3 g gluten-containing study meal
- Gluten degradation by PvP001 in a standardized 3 g gluten-containing study meal following 7 days of standard dose PPI treatment
- Gluten degradation by PvP001 300 mg and PvP001 600 mg in a standardized 1 g gluten-containing study meal at 20, 35, and 65 minutes
- Gluten degradation by PvP001 900 mg in a standardized 6 g gluten-containing study meal at 20, 35, and 65 minutes

Secondary Endpoints:

- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP001
- Plasma concentrations and calculated PK parameters of PvP001
- Development of ADA to PvP001
- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP002
- Plasma concentrations and calculated PK parameters of PvP002
- Development of ADA to PvP002

Part 3

Primary Endpoint:

- Gluten degradation by PvP003 150 mg and 600 mg in a standardized 1 g gluten-containing study meal

Secondary Endpoints:

- Gluten degradation at 35 and 65 minutes by a single dose of PvP003 600 mg with and without pretreatment buffer solution and PvP003 150 mg without pretreatment buffer solution administered before a standardized 1 g gluten-containing study meal
- Gluten degradation at 35 and 65 minutes by a single dose of PvP003 600 mg without pretreatment buffer solution administered after an approximately 50 mL portion of a standardized 1 g gluten-containing study meal
- Gluten degradation at 65 minutes by a single dose PvP003 600 mg without pretreatment buffer solution administered before a standardized gluten-free study meal followed approximately 30 minutes later by a standardized 1 g gluten-containing study meal
- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP003 150 mg and 600 mg after a single dose
- Plasma concentrations and calculated PK parameters of PvP003 150 mg and 600 mg after a single dose
- Development of ADA to PvP003 150 mg and 600 mg after administration of a single dose

Part 4

Primary Endpoint:

- Type, frequency, severity, and relatedness of TEAEs, TESAEs, laboratory abnormalities, changes in ECGs, changes in vital signs, and changes in physical examination findings with PvP003 600 mg after multiple doses

Secondary Endpoints:

- Plasma concentrations and calculated PK parameters of PvP003 600 mg after multiple doses
- Development of ADA to PvP003 600 mg after administration of multiple doses

3.1 Safety Measures

Safety will be assessed by the following:

- Adverse events (AEs)
- Gastrointestinal Symptoms Questionnaires (GSQ)
- Physical examinations
- Vital signs
- Weight assessments
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Anti-drug antibodies (ADA)
- Serum and urine pregnancy tests (in females)
- ECGs

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a four-part, Phase 1, single center study. Each part of the study begins with a Screening Period of up to 4 weeks to allow for completion of Screening procedures and subject scheduling. Each subject will be screened by means of medical history, medication review, GSQ, physical examination, vital signs, weight, height, laboratory tests, and ECG.

Following completion of all Screening procedures, eligible subjects will be enrolled in the study. Part 1 of the study in healthy subjects will be completed prior to enrollment of any subject in Part 2 of the study.

A subject enrolled in Part 1 of the study will participate in one of five dose Cohorts. Healthy subjects will participate in Cohort 1A-1, 1B-1, 1C-1, 1D-1, or 1E-1, and patients with CeD will participate in Cohort 1A-2, 1B-2, 1C-2, 1D-2, or 1E-2. Enrollment of healthy subjects in each of the five dose Cohorts will occur sequentially. Enrollment of patients with CeD in each of the five dose Cohorts will occur sequentially, but each of these dose Cohorts will be open to enrollment only after demonstration of the safety and tolerability of the same dose level in healthy subjects.

A healthy subject enrolled in Part 2 of the study will participate in one of three Groups (Group 1 [Cohorts 2A, 2B, and 2C]), Group 2 [Cohorts 2D and 2E]), or Group 3 [Cohorts 2F and 2G, Cohorts 2F and 2H, or Cohorts 2I and 2J]). Each Group 1 and Group 2 subject will be randomized to the treatment order. Each Group 3 subject will be randomized to the gluten amount in the study meal, the PvP001 dose, and the treatment order. Enrollment of subjects in Group 1, Group 2, and Group 3 may occur in parallel.

A healthy subject enrolled in Part 3 of the study will participate in one of five Groups (Group 1 [Cohorts 3A and 3B], Group 2 [Cohorts 3C and 3D], Group 3 [Cohorts 3E and 3F), Group 4 [Cohorts 3G and 3H], and Group 5 [Cohorts 3I and 3J]). Each Group 1, Group 2, Group 3, and Group 4 subject will be randomized to the treatment order. Enrollment of subjects in Group 1, Group 2, Group 3, Group 4, and Group 5 will occur sequentially.

A healthy subject enrolled in Part 4 of the study will participate in two Cohorts (Cohort 4A and Cohort 4B). Each Part 4 subject will be randomized to the treatment order. Enrollment of subjects in Part 4 may occur in parallel with enrollment of subjects in Part 3.

Subjects who participate in Part 1 or Part 2 of the study, and who are not ADA positive, may participate in Part 3 or Part 4 of the study. No other subjects may participate in more than one Part/Group of the study.

Part 1

This is a single-blind, placebo-controlled, single ascending dose study of PvP001, followed by administration of a single dose of the MFD of PvP002, in healthy adult subjects and adult patients with well controlled CeD.

A single dose of PvP001 placebo, PvP001 100 mg, PvP001 300 mg, or PvP001 900 mg will be administered in ascending order to healthy subjects in Cohorts 1A-1, 1B-1, 1C-1, and 1D-1, and to patients with CeD in Cohorts 1A-2, 1B-2, 1C-2, and 1D-2, respectively. A single dose of the MFD of PvP002 will then be administered to healthy subjects in Cohort 1E-1 and to patients with CeD in Cohort 1E-2. Each subject will participate in only one of the five dose Cohorts and will be blinded to the PvP001 and PvP002 dose (PvP001 placebo, PvP001 100 mg, PvP001 300 mg, PvP001 900 mg, or MFD of PvP002). The MFD of PvP002 will not exceed the MTD of PvP001.

Table 1 lists the number of subjects in each Cohort in Part 1 of the study.

Table 1. Part 1 (Single Ascending Dose)

PvP001 (mg)	Healthy Subject Cohort	Number of Healthy Subjects per Cohort	Celiac Disease Patient Cohort	Number of Patients with Celiac Disease per Cohort
0	1A-1	3-6	1A-2	3-6
100	1B-1	3-6	1B-2	3-6
300	1C-1	3-6	1C-2	3-6
900	1D-1	3-6	1D-2	3-6
PvP002 (mg)				
MFD	1E-1	3-6	1E-2	3-6

MFD = maximum feasible dose

Enrollment in each of the five dose Cohorts will begin with healthy subjects in Cohort 1A-1 and will proceed sequentially through Cohort 1E-1 according to the dose escalation guidelines below. Dose-limiting toxicity (DLT) will be defined as a study drug-related serious AE (SAE) or a study drug-related AE of Grade 2 or higher based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03[1].

- 3 subjects will be treated at the given PvP001 dose level and the safety data through the Safety Follow Up Call will be reviewed
  - If 0 of these 3 subjects experiences DLT, enrollment of subjects at the next higher dose level will begin
  - If 1 of these 3 subjects experiences DLT, 3 additional subjects will be enrolled at this same dose level
    - If 1 of 6 total subjects at this dose level experiences DLT, enrollment of subjects at the next higher dose level will begin
    - If ≥2 of 6 total subjects at this dose level experience DLT, the MTD will have been exceeded
      - If 6 total subjects were not enrolled at the previous dose level, and the previous dose level was 100 mg or 300 mg, 3 additional subjects will be enrolled at the

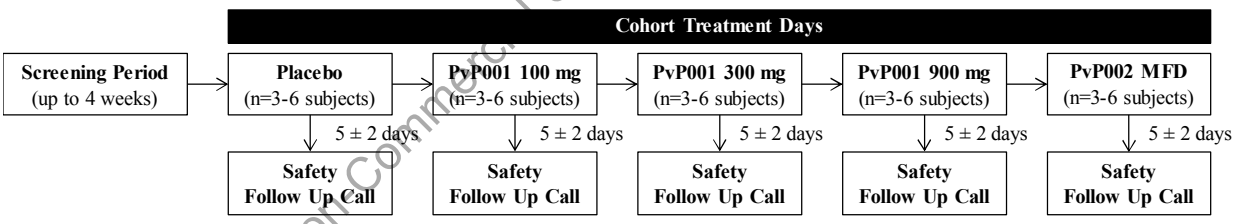
previous dose level to demonstrate DLT in <2 of 6 subjects and establish this as the MTD of PvP001 to be used in Part 2

- 3 subjects will be treated with the MFD of PvP002 and the safety data through the Safety Follow Up Call will be reviewed
  - If 0 of these 3 subjects experiences DLT, the MFD of PvP002 will be used in Part 2
  - If 1 of these 3 subjects experiences DLT, 3 additional subjects will be treated with the MFD of PvP002
    - If 1 of 6 total subjects treated with the MFD of PvP002 experiences DLT, the MFD of PvP002 will be used in Part 2
    - If ≥2 of 6 total subjects treated with the MFD of PvP002 experience DLT, the MFD of PvP002 will not be used in Part 2

Once a given PvP001 dose level or the MFD of PvP002 is deemed safe in healthy subjects based on these guidelines, enrollment of patients with CeD will begin at this dose level and will proceed according to the same dose escalation guidelines. This may occur simultaneously with enrollment of healthy subjects in the next higher PvP001 dose Cohort or in the MFD of PvP002 Cohort. Patients with CeD enrolled in Part 1 of the study will only be administered dose levels of PvP001 or PvP002 that have previously been deemed safe and well tolerated in healthy subjects.

The Part 1 study design is depicted in the schematic in Figure 1.

Figure 1. Part 1 Study Visit Schematic



MFD = maximum feasible dose

Note: Blood sample for anti-drug antibody testing will be obtained 14 ± 2 and 28 ± 2 days after the Cohort Treatment Day.

Each subject will report to the Clinical Research Center the afternoon prior to the Cohort Treatment Day (i.e., on Cohort Treatment Day -1). The subject will eat a gluten-free dinner at the Clinical Research Center and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours). Pretreatment buffer solution (to raise the fasting gastric pH to a level above which the enzyme in PvP001 and PvP002 is stable), followed by study drug, will be administered orally immediately prior to beginning the ingestion of a standardized gluten-free study meal. The entire study meal will be ingested within 10 minutes of study drug administration.

A blood sample will be obtained before pretreatment buffer solution administration, at several time points for approximately 480 minutes (8 hours) after study drug administration on the Cohort Treatment Day, and at the 24-Hour Safety Assessment approximately 24 hours after study drug administration to evaluate systemic exposure to PvP001 and PvP002.

Ice chips (a maximum of 240 mL up to every hour) may be ingested beginning one hour after study drug administration and continuing until ad libitum ingestion of food and liquids begins. Ingestion of food and liquids (normal diet in a healthy subject and gluten-free diet in a patient with CeD) ad libitum may begin approximately 185 minutes after study drug administration, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. The subject will begin an overnight fast (nothing by mouth except water for at least 12 hours) prior to the 24-Hour Safety Assessment.

The 24-Hour Safety Assessment will occur for each subject approximately 24 hours after study drug administration. Each subject will be discharged from the Clinical Research Center following completion of the 24-Hour Safety Assessment, and when the Investigator determines that the subject is in stable condition.

A Safety Follow Up Call will occur for each subject 5 ± 2 days after the 24-Hour Safety Assessment. At the discretion of the Investigator, the subject will return to the Clinical Research Center for a safety follow up visit and/or a safety follow up procedure(s) (e.g., clinical laboratory tests).

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day to test for ADA to PvP001 and PvP002. In a subject who develops ADA, the ADA level will be monitored until it returns to the pre-dose baseline.

Part 2

This is a single-blind, placebo-controlled, single dose study of PvP001 and PvP002 using gastric sample aspiration to evaluate gluten degradation in healthy adult subjects under the following conditions: (a) In Group 1, administration of PvP001 placebo, the MTD of PvP001, and the MTD of PvP001 following 7 days of PPI treatment, before a standardized 3 g gluten-containing study meal, (b) In Group 2, administration of the PvP002 comparator (sterile water) and the MFD of PvP002, before a standardized 3 g gluten-containing study meal, and (c) In Group 3, administration of PvP001 placebo, PvP001 300 mg, and PvP001 600 mg before a standardized 1 g gluten-containing study meal, and administration of PvP001 900 mg before a standardized 6 g gluten-containing study meal. (Note: The MTD of PvP001 in healthy volunteers has been determined to be 900 mg and has been administered to Group 1 healthy volunteers before a 3 g gluten-containing study meal. This dose of PvP001 and placebo will be administered before a higher [6 g] gluten-containing meal, and two lower doses [300 mg and 600 mg] of PvP001 and placebo will be administered before a lower [1 g] gluten-containing meal, in Group 3 healthy volunteers.)

Twelve subjects will participate in Group 1 and will receive PvP001 placebo, the MTD of PvP001, and the MTD of PvP001 following 7 days of treatment with a standard dose of a PPI; each of these 12 subjects will receive all three treatments, but will be randomized to the treatment order. Group 1 subjects will be blinded to the PvP001 dose (placebo or the MTD).

Ten unique subjects will participate in Group 2 and will receive the PvP002 comparator (sterile water) and the MFD of PvP002; each of these 10 subjects will receive both treatments, but will be randomized to the treatment order. Group 2 subjects will be blinded to which of the two treatments is active study drug.

Twenty-four unique subjects will participate in Group 3. Each subject will receive two treatments, but will be randomized to the treatment order. Eight subjects will be randomized to receive a 1 g gluten-containing study meal; the two treatments will be PvP001 placebo and PvP001 300 mg. Eight subjects will be randomized to receive a 1 g gluten-containing study meal; the two treatments will be PvP001 placebo and PvP001 600 mg. Eight subjects will be randomized to receive a 6 g gluten-containing study meal; the two treatments will be PvP001 placebo and PvP001 900 mg. Group 3 subjects will be blinded to the PvP001 dose (placebo, 300 mg, 600 mg, or 900 mg) and to the amount of gluten in the study meal.

A subject may not participate in more than one Group. Enrollment of subjects in Group 1, Group 2, and Group 3 may occur in parallel.

Table 2 lists the number of subjects and the Cohorts within Group 1, Group 2, and Group 3 in Part 2 of the study.

Table 2. Part 2 (Gluten Degradation)

Group	Cohort	PvP001 (mg)	Number of Healthy Subjects per Group
1[a]	2A	0	12
	2B	MTD	
	2C	MTD with PPI	
		PvP002 (mg)	
2[a]	2D	0	10
	2E	MFD	
		PvP001 (mg)	
3[b]	2F	0	24
	2G	300	
	2H	600	
	2I	0	
	2J	900	

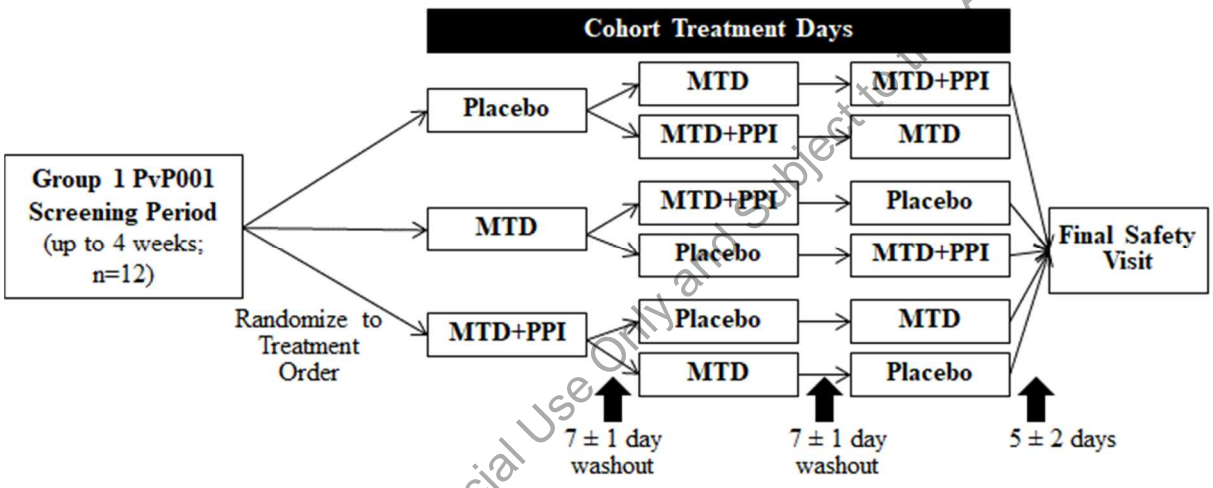
MFD = maximum feasible dose; MTD = maximum tolerated dose; PPI = proton pump inhibitor
[a] Group 1 and Group 2 subjects will ingest a standardized 3 g gluten-containing study meal.
[b] Group 3 Cohort 2F, 2G, and 2H subjects will ingest a standardized 1 g gluten-containing study meal; Group 3 Cohort 2I and 2J will ingest a standardized 6 g gluten-containing study meal.

A subject enrolled in Group 1, Group 2, or Group 3 will participate in each Cohort Treatment Day sequentially, in the treatment order to which the subject was randomized, unless one of the individual subject stopping criteria below is met. In this case, the subject will be withdrawn from the study.

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

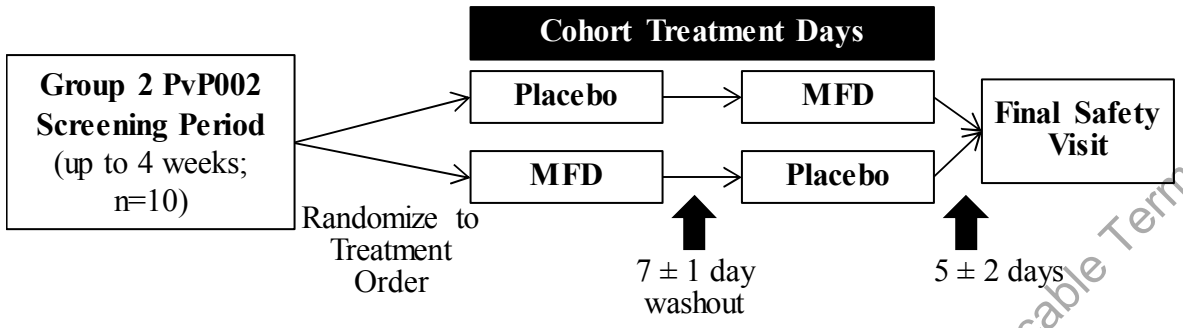
The Part 2 study design is depicted in the schematics in Figure 2.

Figure 2. Part 2 Study Visit Schematic

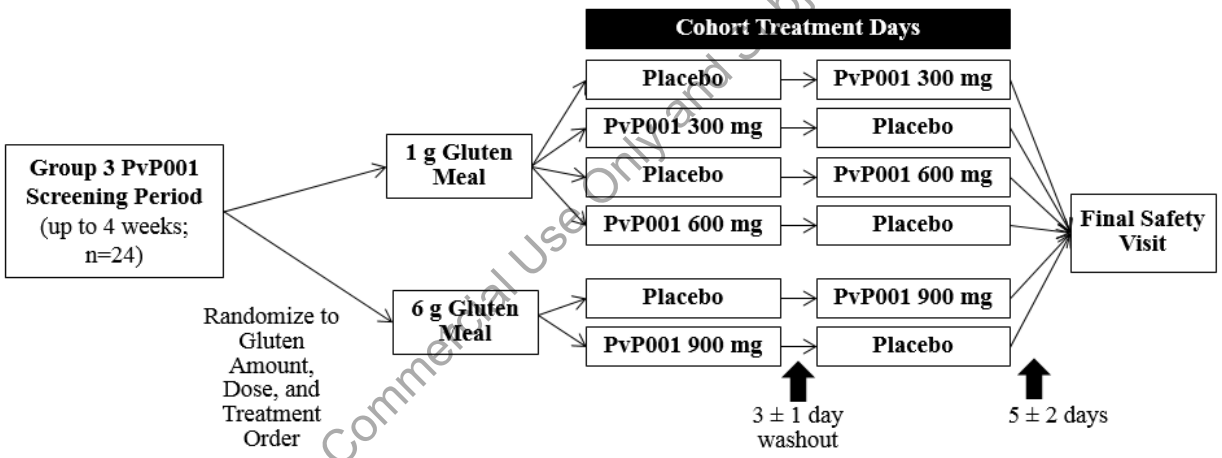


MTD = maximum tolerated dose; PPI = proton pump inhibitor
Note: Blood sample for anti-drug antibody testing will be obtained 14 ± 2 and 28 ± 2 days after the final Cohort Treatment Day.

Figure 2. Part 2 Study Visit Schematic (Continued)



MFD = maximum feasible doser
Note: Blood sample for anti-drug antibody testing will be obtained 14 ± 2 and 28 ± 2 days after the final Cohort Treatment Day.



Note: Blood sample for anti-drug antibody testing will be obtained 14 ± 2 and 28 ± 2 days after the final Cohort Treatment Day.

Each subject will report to the Clinical Research Center the afternoon prior to each Cohort Treatment Day (i.e., on Cohort Treatment Day -1). The subject will eat a gluten-free dinner at the Clinical Research Center and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

On each Cohort Treatment Day, a single-lumen catheter (nasogastric [NG] tube) will be introduced into the stomach. Auscultation and gastric pH testing will be used to confirm tube placement.

Pretreatment buffer solution, followed by study drug, will be administered orally immediately prior to beginning the ingestion of a standardized 3 g gluten-containing study meal (Group 1 and

Group 2) or a standardized 1 g gluten-containing or 6 g gluten-containing study meal (Group 3). The entire study meal will be ingested within 10 minutes of study drug administration.

The use of the NG tube will facilitate aspiration of gastric contents to measure the concentration of gluten (i.e., to assess gluten degradation). A gastric sample (approximately 5 mL) will be obtained via the NG tube before pretreatment buffer solution administration. A gastric sample (entire gastric content) will be obtained via the NG tube 35 minutes after study drug administration in a Group 1 and Group 2 subject. A gastric sample (approximately 5 mL) will be obtained via the NG tube 20 and 35 minutes after study drug administration, and a gastric sample (entire gastric content) will be obtained via the NG tube 65 minutes after study drug administration, in a Group 3 subject. Gastric pH testing will also be performed on these samples; the pH of the gastric sample obtained before pretreatment buffer solution administration will be used to confirm that the NG tube is in the stomach and will serve as the pretreatment pH measurement. The aspirated volume of the entire gastric content sample obtained 35 minutes after study drug administration in a Group 1 and Group 2 subject and 65 minutes after study drug administration in a Group 3 subject will be measured before a portion is removed for pH testing and gluten quantification.

A blood sample will be obtained before pretreatment buffer solution administration and at several time points for approximately 480 minutes (8 hours) after study drug administration on each Cohort Treatment Day to evaluate systemic exposure to PvP001 and PvP002.

A urine sample will be obtained before and approximately 240 minutes after study drug administration on each Cohort Treatment Day in a Group 3 subject to test for gluten immunogenic peptides, provided the subject consents to this.

Ingestion of food and liquids (normal diet) ad libitum may begin approximately 185 minutes after study drug administration in a Group 1 and Group 2 subject and ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration in a Group 3 subject, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides) in a Group 3 subject. The NG tube will have been removed prior to the ingestion of food and liquids (normal diet) ad libitum in a Group 1 and Group 2 subject and prior to the ingestion of plain gluten-free food and liquids in a Group 3 subject.

Each subject will be discharged from the Clinical Research Center following completion of all study procedures on each Cohort Treatment Day, and when the Investigator determines that the subject is in stable condition. Each subject will have a washout period of 7 ± 1 days (Group 1 and Group 2) or 3 ± 1 days (Group 3) between Cohort Treatment Days.

A Safety Visit will occur for each Part 2 subject 5 ± 2 days after the final Cohort Treatment Day, or 5 ± 2 days after the subject's last Cohort Treatment Day for a subject who withdraws early from the study.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day to test for ADA to PvP001 and PvP002. In a subject who develops ADA, the ADA level will be monitored until it returns to the pre-dose baseline.

Part 3

This is a single-blind, placebo-controlled, single dose study of PvP003 using gastric sample aspiration to evaluate gluten degradation in healthy adult subjects under the following conditions: (a) In Group 1, administration of PvP003 placebo and PvP003 600 mg with pretreatment buffer solution before a standardized 1 g gluten-containing study meal, (b) In Group 2, administration of PvP003 placebo and PvP003 600 mg without pretreatment buffer solution before a standardized 1 g gluten-containing study meal, (c) In Group 3, administration of PvP003 placebo and PvP003 600 mg without pretreatment buffer solution after an approximately 50 mL portion of a standardized 1 g gluten-containing study meal, (d) In Group 4, administration of PvP003 placebo and PvP003 600 mg without pretreatment buffer solution before a standardized gluten-free study meal followed approximately 30 minutes later by a standardized 1 g gluten-containing study meal, and (e) In Group 5, administration of PvP003 placebo and PvP003 150 mg without pretreatment buffer solution before a standardized 1 g gluten-containing study meal. Data from both the 600 mg dose and the 150 mg split tablet dose will provide data on activity across the expected clinically relevant dose range to inform future formulation development and doses for inclusion in planned clinical trials.

Thirty-six unique subjects (6 subjects in each of the following four Groups: Group 1, Group 2, Group 3, and Group 4, and 12 subjects in Group 5) will participate in Part 3 and will receive PvP003 placebo and PvP003 150 mg or 600 mg as noted in Table 3; each of these 36 subjects will receive both treatments, but will be randomized to the treatment order. Part 3 subjects will be blinded to which of the two treatments is active study drug.

A subject may not participate in more than one Group. Enrollment of subjects in Group 1, Group 2, Group 3, Group 4, and Group 5 will occur sequentially.

Table 3 lists the number of subjects and the Cohorts within Group 1, Group 2, Group 3, Group 4, and Group 5 in Part 3 of the study.

Table 3. Part 3 (Gluten Degradation)

Group	Cohort	PvP003 (mg)	Pretreatment Buffer Solution Administered	Number of Healthy Subjects per Group
1[a]	3A	0	Yes	6
	3B	600	Yes	
2[a]	3C	0	No	6
	3D	600	No	
3[a]	3E	0	No	6
	3F	600	No	
4[b]	3G	0	No	6
	3H	600	No	
5[a]	3I	0	No	12
	3J	150	No	

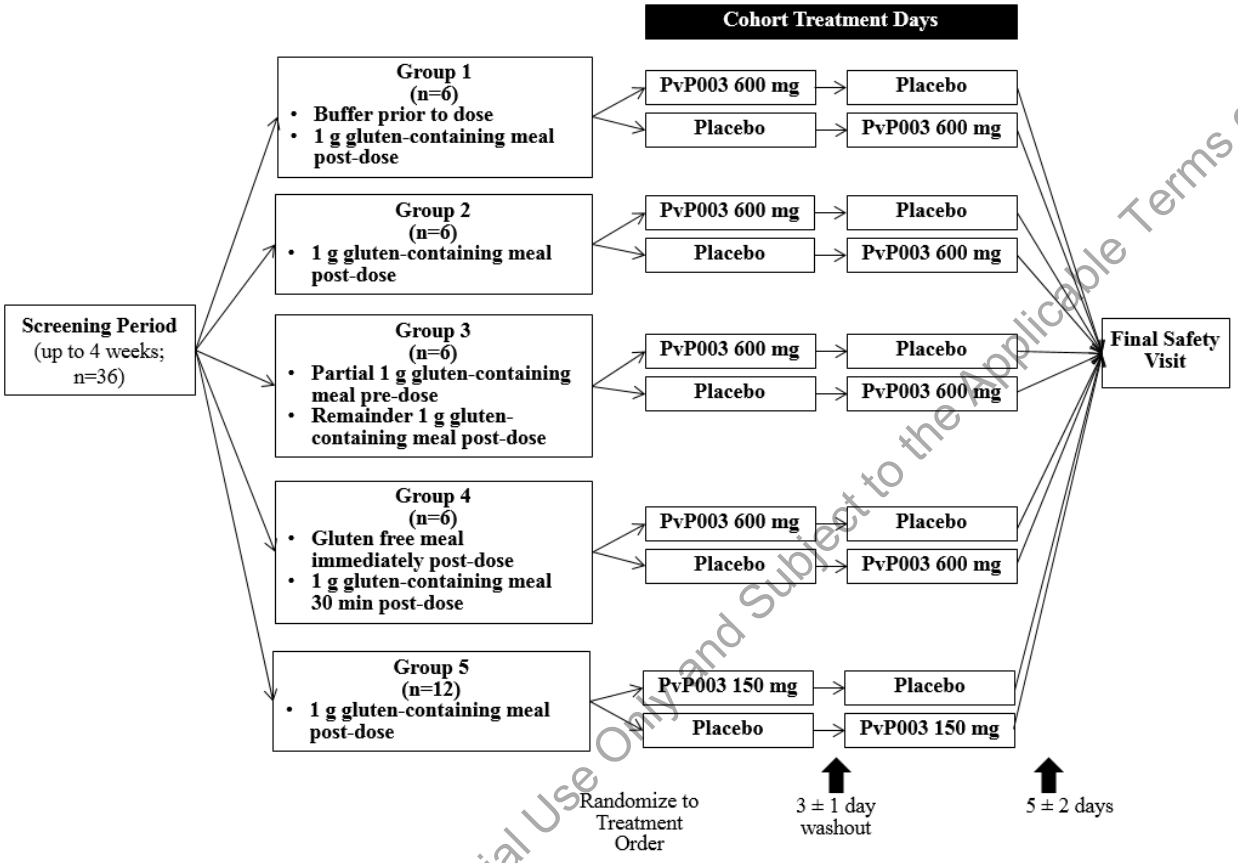
[a] Group 1, Group 2, Group 3, and Group 5 subjects will ingest a standardized 1 g gluten-containing study meal.
[b] Group 4 subjects will ingest a standardized gluten-free study meal followed by a standardized 1 g gluten-containing study meal.

A subject enrolled in Group 1, Group 2, Group 3, Group 4, or Group 5 will participate in each Cohort Treatment Day sequentially, in the treatment order to which the subject was randomized, unless one of the individual subject stopping criteria below is met. In this case, the subject will be withdrawn from the study.

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

The Part 3 study design is depicted in the schematic in Figure 3.

Figure 3. Part 3 Study Visit Schematic



Note: Blood sample for anti-drug antibody testing will be obtained 14 ± 2 and 28 ± 2 days after the final Cohort Treatment Day.

Each subject will report to the Clinical Research Center the afternoon prior to each Cohort Treatment Day (i.e., on Cohort Treatment Day -1). The subject will eat a gluten-free dinner at the Clinical Research Center and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

On each Cohort Treatment Day, a single-lumen catheter (nasogastric [NG] tube) will be introduced into the stomach. Auscultation and gastric pH testing will be used to confirm tube placement.

Group 1

Pretreatment buffer solution, followed by study drug, will be administered orally immediately prior to beginning the ingestion of a standardized 1 g gluten-containing study meal. The entire study meal will be ingested within 10 minutes of study drug administration.

Group 2 and Group 5

Study drug will be administered orally immediately prior to beginning the ingestion of a standardized 1 g gluten-containing study meal. The entire study meal will be ingested within 10 minutes of study drug administration. No pretreatment buffer solution will be administered.

Group 3

An approximately 50 mL portion of a standardized 1 g gluten-containing study meal will be ingested within 5 minutes. Study drug will be administered orally immediately after completing the ingestion of the approximately 50 mL portion of the study meal (this is approximately one sixth of the entire study meal). The remaining portion of the standardized 1 g gluten-containing study meal will begin to be ingested immediately after study drug administration; this remaining portion of the study meal will be ingested within 10 minutes of study drug administration. No pretreatment buffer solution will be administered.

Group 4

Study drug will be administered orally immediately prior to beginning the ingestion of a standardized gluten-free study meal. The entire gluten-free study meal will be ingested within 10 minutes of study drug administration. A standardized 1 g gluten-containing study meal will begin to be ingested 30 minutes after study drug administration. The entire gluten-containing study meal will be ingested within 10 minutes. No pretreatment buffer solution will be administered.

Group 1, Group 2, Group 3, Group 4, and Group 5

The use of the NG tube will facilitate aspiration of gastric contents to measure the concentration of gluten (i.e., to assess gluten degradation). A gastric sample (approximately 5 mL) will be obtained via the NG tube before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3). A gastric sample (approximately 15 mL) will be obtained via the NG tube 35 minutes after study drug administration in a Group 1, Group 2, Group 3, and Group 5 subject. A gastric sample (entire gastric content) will be obtained 65 minutes after study drug administration in a Group 1, Group 2, Group 3, Group 4, and Group 5 subject. Gastric pH testing will also be performed on these samples; the pH of the gastric sample obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3) will be used to confirm that the NG tube is in the stomach and will serve as the pretreatment pH measurement. The aspirated volume of the entire gastric content sample obtained 65 minutes after study drug administration in a Group 1, Group 2, Group 3, Group 4, and Group 5 subject will be measured before a portion is removed for pH testing and gluten quantification.

A blood sample will be obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3), and at several time

points for approximately 480 minutes (8 hours) after study drug administration on each Cohort Treatment Day to evaluate systemic exposure to PvP003.

A urine sample will be obtained before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3), and approximately 240 minutes after study drug administration on each Cohort Treatment Day to test for gluten immunogenic peptides, provided the subject consents to this.

Ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides). The NG tube will have been removed prior to the ingestion of plain gluten-free food and liquids.

Each subject will be discharged from the Clinical Research Center following completion of all study procedures on each Cohort Treatment Day, and when the Investigator determines that the subject is in stable condition. Each subject will have a washout period of 3 ± 1 days between Cohort Treatment Days.

A Safety Visit will occur 5 ± 2 days after the final Cohort Treatment Day, or 5 ± 2 days after the subject's last Cohort Treatment Day for a subject who withdraws early from the study.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day to test for ADA to PvP003. In a subject who develops ADA, the ADA level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first.

Part 4

This is a single-blind, placebo-controlled, multiple dose study of PvP003 in healthy adult subjects to evaluate safety following repeated administrations.

Six unique subjects will participate in Part 4 and will receive PvP003 placebo and PvP003 600 mg; each of these 6 subjects will receive both treatments three times a day (TID) for 5 days, but will be randomized to the treatment order. Part 4 subjects will be blinded to which of the two treatments is active study drug. No pretreatment buffer solution will be administered.

Enrollment of subjects in Part 4 may occur in parallel with enrollment of subjects in Part 3.

Table 4 lists the number of subjects and the Cohorts in Part 4 of the study.

Table 4. Part 4 (Multiple Doses)

Cohort	PvP003 (mg) TID X 5 Days	Number of Healthy Subjects
4A	0	6
4B	600	

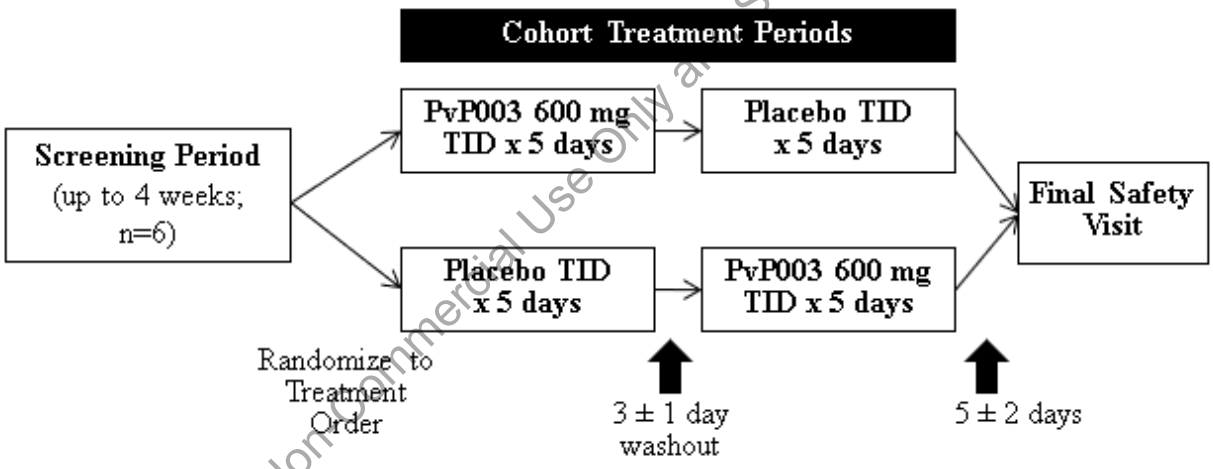
TID = three times a day

A subject enrolled in Part 4 will participate in each 5-day Cohort Treatment Period sequentially, in the treatment order to which the subject was randomized, unless one of the individual subject stopping criteria below is met. In this case, the subject will be withdrawn from the study.

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

The Part 4 study design is depicted in the schematic in Figure 4.

Figure 4. Part 4 Study Visit Schematic



TID = three times a day
Note: Blood sample for anti-drug antibody testing will be obtained 14 ± 2 and 28 ± 2 days after the final Cohort Treatment Day.

Each subject will report to the Clinical Research Center the afternoon prior to Day 1 and Day 5 of each Cohort Treatment Period. On Day 1 and Day 5 of each Cohort Treatment Period, the first daily dose of study drug (PvP003 placebo or PvP003) will be administered orally by study personnel immediately prior to the subject beginning the ingestion of a regular meal (i.e., breakfast).

A blood sample will be obtained before and at several time points for approximately 240 minutes (4 hours) after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period to evaluate systemic exposure to PvP003.

A urine sample will be obtained before the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period to test for gluten immunogenic peptides, provided the subject consents to this.

Ingestion of any type of snack food and liquids may begin approximately 135 minutes after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of a regular meal (i.e., lunch) may begin approximately 255 minutes after administration of the first daily dose of study drug (i.e., after completion of the 240-minute post-dose PK sampling and clinical laboratory tests [Day 1], or after completion of the 240-minute post-dose PK sampling [Day 5], and immediately after administration of the second daily dose of study drug) on Day 1 and Day 5 of each Cohort Treatment Period.

Each subject will be discharged from the Clinical Research Center following completion of all study procedures on Day 1 and Day 5 of each Cohort Treatment Period, and when the Investigator determines that the subject is in stable condition. After discharge on Day 1 of each Cohort Treatment Period (i.e., beginning with the third daily dose of study drug on Day 1), study drug will be self-administered TID before regular meals (i.e., breakfast, lunch, and dinner) until the subject is admitted to the Clinical Research Center on Day 4 of each Cohort Treatment Period (i.e., after the second daily dose of study drug on Day 4). Each subject will have a washout period of 3 ± 1 days between the two Cohort Treatment Periods (i.e., between Day 5 of the first Cohort Treatment Period and Day 1 of the second Cohort Treatment Period).

A Safety Visit will occur 5 ± 2 days after Day 5 of the second Cohort Treatment Period, or 5 ± 2 days after the subject's last dose of study drug for a subject who withdraws early from the study.

A blood sample will be obtained at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after Day 5 of the second Cohort Treatment Period to test for ADA to PvP003. In a subject who develops ADA, the ADA level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first.

4.2 Number of Subjects

Part 1

Approximately 15-30 eligible healthy subjects and 15-30 eligible patients with CeD will participate in Part 1 of the study (i.e., approximately 3-6 healthy subjects will participate in each of five dose Cohorts and approximately 3-6 patients with CeD will participate in each of five dose Cohorts).

Part 2

Approximately 46 eligible healthy subjects will participate in Part 2 of the study (i.e., approximately 12 subjects will participate in Group 1, approximately 10 subjects will participate in Group 2, and approximately 24 subjects will participate in Group 3).

Part 3

Approximately 36 eligible healthy subjects will participate in Part 3 of the study (i.e., approximately 6 subjects each in Group 1, Group 2, Group 3, and Group 4, and approximately 12 subjects in Group 5).

Part 4

Approximately 6 eligible healthy subjects will participate in Part 4 of the study.

4.3 Duration of Study

Each part of the study begins with a Screening Period of up to 4 weeks to allow for completion of Screening procedures and subject scheduling.

Part 1

Each subject will participate in the study for up to approximately 8 weeks, including the Screening Period, Cohort Treatment Day with post-dose 24-Hour Safety Assessment, Safety Follow Up Call 5 ± 2 days after the 24-Hour Safety Assessment, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day.

Part 2

Each subject enrolled in Group 1 will participate in the study for up to approximately 10 weeks, including the Screening Period, three Cohort Treatment Days, washout period of 7 ± 1 days between each of the Cohort Treatment Days, Safety Visit 5 ± 2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visit 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Each subject enrolled in Group 2 will participate in the study for up to approximately 9 weeks, including the Screening Period, two Cohort Treatment Days, washout period of 7 ± 1 days between each of the Cohort Treatment Days, Safety Visit 5 ± 2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Each subject enrolled in Group 3 will participate in the study for up to approximately 9 weeks, including the Screening Period, two Cohort Treatment Days, washout period of 3 ± 1 days between each of the Cohort Treatment Days, Safety Visit 5 ± 2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Part 3

Each subject will participate in the study for up to approximately 9 weeks, including the Screening Period, two Cohort Treatment Days, washout period of 3 ±1 days between each of the Cohort Treatment Days, Safety Visit 5 ±2 days after the final Cohort Treatment Day, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day.

Part 4

Each subject will participate in the study for up to approximately 10 weeks, including the Screening Period, two 5-day Cohort Treatment Periods, washout period of 3 ±1 days between the two Cohort Treatment Periods, Safety Visit 5 ±2 days after Day 5 of the second Cohort Treatment Period, and Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after Day 5 of the second Cohort Treatment Period.

4.4 Schedule of Assessments

Study visits will be conducted as described in the Schedule of Assessments (see Table 5, Table 6, Table 7, and Table 8).

Table 5. Part 1 Schedule of Assessments

Procedure	Screening Period[a]	Cohort Treatment Day -1[b]	Cohort Treatment Day[c]		24-Hour Safety Assessment[d]	Safety Follow Up Call[e]	Follow Up Anti-Drug Antibody Blood Sampling Visits
			Pre-Dose	Post-Dose			
Informed consent	X						
Inclusion and exclusion criteria review	X		X				
Medical history review	X	X	X				
Vital signs[f]	X		X	X[g]	X		
Weight	X		X				
Height	X						
Body mass index calculation	X						
Physical examination	X		X	X[h]	X		
Intravenous catheter placement			X				
Pharmacokinetic blood sampling			X	X[i]	X		
Anti-drug antibody blood sampling	X						X[j]
Gluten-free diet confirmation		X	X				
Gastrointestinal Symptoms Questionnaire	X		X	X[k]	X		
Clinical laboratory tests	X[l]		X[l]	X[m]	X[l]		
Serum immunoglobulin A antibodies to tissue transglutaminase and total immunoglobulin A[n]	X						
Serum pregnancy test[o]	X	X					
Urine drug screen	X	X					
Alcohol breathalyzer test	X	X					
Helicobacter pylori breath test	X						
Electrocardiogram	X		X	X[p]	X		
Concomitant medication review[q]	X	X	X	X	X	X	X
Adverse event recording[r]				X[s]	X	X	X[t]

[a] Screening Period of up to 4 weeks.
[b] Subject will be admitted to the Clinical Research Center the afternoon prior to the Cohort Treatment Day.
[c] Cohort 1A-1, 1B-1, 1C-1, 1D-1, or 1E-1 Treatment Day for a healthy subject; Cohort 1A-2, 1B-2, 1C-2, 1D-2, or 1E-2 for a patient with celiac disease.
[d] 24-Hour Safety Assessment will be performed approximately 24 hours after study drug administration.
[e] Safety Follow Up Call will be performed 5 ± 2 days after the 24-Hour Safety Assessment.
[f] Vital signs will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.
[g] Vital signs will be obtained approximately 70, 190, and 270 minutes after study drug administration.
[h] Complete physical examination will be performed approximately 275 minutes after study drug administration.
[i] Blood sample for pharmacokinetics will be obtained approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration.
[j] Blood sample for anti-drug antibody testing will be obtained 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day. In a subject who develops anti-drug antibodies, the anti-drug antibody level will be monitored until it returns to the pre-dose baseline.
[k] Gastrointestinal Symptoms Questionnaire will be completed approximately 30, 130, and 325 minutes after study drug administration.
[l] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained in the 12-hour fasting state (water will be allowed during the 12-hour period before the Screening and 24-Hour Safety Assessment clinical laboratory tests, but not during the 12-hour period before the Cohort Treatment Day pre-dose clinical laboratory tests).
[m] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained approximately 240 minutes after study drug

administration; urinalysis may be done at later time point (up to 480 minutes after study drug administration), if necessary.

[n] Patient with celiac disease only.

[o] Female subject only.

[p] Electrocardiogram will be performed approximately 285 minutes after study drug administration.

[q] All medications used from 7 days prior to the Screening Visit through the Safety Follow Up Call will be recorded. If a subject spontaneously reports an adverse event after the Safety Follow Up Call through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit, concomitant medication will be recorded.

[r] Adverse event recording will begin after study drug administration on the Cohort Treatment Day.

[s] Adverse event recording will be performed at approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report.

[t] Spontaneously reported adverse events will be recorded after the Safety Follow Up Call through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.

Table 6. Part 2 Schedule of Assessments

Procedure	Screening Period[a]	Cohort Treatment Day -1[b]	Cohort Treatment Days[c,d]		Safety Visit[e]	Follow Up Anti-Drug Antibody Blood Sampling Visits
			Pre-Dose	Post-Dose		
Informed consent	X					
Inclusion and exclusion criteria review	X		X			
Medical history review	X	X[f]	X[g]			
Vital signs[h]	X		X[i]	X[j]	X	
Weight	X		X		X	
Height	X					
Body mass index calculation	X					
Physical examination	X		X	X[k]	X	
Randomization	X					
Intravenous catheter placement			X			
Pharmacokinetic blood sampling			X	X[l]		
Dispense Nexium and Daily Nexium Dosing Diary	X[m]			X[n]		
Nexium return inventory and Daily Nexium Dosing Diary review		X				
Gluten-free diet confirmation		X	X			
Gastrointestinal Symptoms Questionnaire	X		X[o]	X[p]		
Nasogastric tube placement			X			
Nasogastric tube removal				X[q]		
Gastric sampling			X[r]	X[s]		
Anti-drug antibody blood sampling	X					X[t]
Clinical laboratory tests	X[u]		X[u]	X[v]	X[u]	
Pregnancy test	X[w]	X[w,x]			X[w]	
Urine drug screen	X	X			X	
Alcohol breathalyzer test	X	X			X	
Helicobacter pylori breath test	X					
Electrocardiogram	X		X	X[y]	X	
Concomitant medication review[z]	X	X	X	X	X	X
Adverse event recording[aa]		X[bb]	X[cc]	X[dd]	X	X[ee]
Urine sample for gluten immunogenic peptides[ff]			X	X[gg]		

[a] Screening Period of up to 4 weeks.
[b] Subject will be admitted to the Clinical Research Center the afternoon prior to each Cohort Treatment Day.
[c] Group 1 Cohorts 2A, 2B, and 2C Treatment Days; Group 2 Cohorts 2D and 2E Treatment Days; Group 3 Cohorts 2F, 2G, 2H, 2I, and 2J Treatment Days.
[d] Each subject will have a washout period of 7 ± 1 days (Group 1 and Group 2) or 3 ± 1 days (Group 3) between Cohort Treatment Days.
[e] Safety Visit will be performed 5 ± 2 days after the final Cohort Treatment Day, or 5 ± 2 days after the subject's last Cohort Treatment Day for a subject who withdraws early from the study.
[f] Medical history review will be performed on the first Cohort Treatment Day -1.
[g] Medical history review will be performed before nasogastric tube placement on the first Cohort Treatment Day.
[h] Vital signs will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.
[i] Vital signs will be completed before nasogastric tube placement and after nasogastric tube placement (i.e., before pretreatment buffer solution administration).
[j] Vital signs will be obtained approximately 70, 190, and 270 minutes after study drug administration.
[k] Complete physical examination will be performed approximately 275 minutes after study drug administration.
[l] Blood sample for pharmacokinetics will be obtained approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration.
[m] Nexium and Daily Nexium Dosing Diary will be dispensed at Screening to a Group 1 subject randomized to Cohort 2C first.
[n] Nexium and Daily Nexium Dosing Diary will be dispensed upon discharge from the Clinical Research Center on the Cohort Treatment Day prior to the Cohort 2C Treatment Day to a Group 1 subject not randomized to Cohort 2C first.
[o] Gastrointestinal Symptoms Questionnaire will be completed before nasogastric tube placement and after nasogastric tube placement (i.e., before pretreatment buffer solution administration).
[p] Gastrointestinal Symptoms Questionnaire will be completed approximately 30, 130, and 325 minutes after study drug administration.
[q] Nasogastric tube will be removed approximately 135 minutes after study drug administration in a Group 1 and Group 2 subject and approximately 80 minutes after study drug administration in a Group 3 subject.
[r] Gastric sample (approximately 5 mL) will be obtained after nasogastric tube placement for pH testing (to confirm tube placement and serve as pretreatment pH measurement) and gluten quantification.
[s] Gastric sample (entire gastric content) will be obtained 35 minutes after study drug administration in a Group 1 and Group 2 subject for pH testing and gluten quantification. Gastric sample (approximately 5 mL) will be obtained 20 and 35 minutes after study drug administration, and gastric sample (entire gastric content) will be obtained 65 minutes after study drug administration, in a Group 3 subject for pH testing and gluten quantification. The aspirated volume of the entire gastric content sample obtained 35 minutes after study drug administration in a Group 1 and Group 2 subject and 65 minutes after study drug administration in a Group 3 subject will be measured before a portion is removed for pH testing and gluten quantification.
[t] Blood sample for anti-drug antibody testing will be obtained 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day. In a subject who develops anti-drug antibodies, the anti-drug antibody level will be monitored until it returns to the pre-dose baseline.
[u] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained in the 12-hour fasting state (water will be allowed during the 12-hour period before the Screening and Safety Visit clinical laboratory tests, but not during the 12-hour period before the Cohort Treatment Day pre-dose clinical laboratory tests).
[v] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained approximately 240 minutes after study drug administration; urinalysis may be done at later time point (up to 480 minutes after study drug administration), if necessary.
[w] Serum pregnancy test will be performed in a female at Screening, on the first Cohort Treatment Day -1, and at the Safety Visit.
[x] Urine pregnancy test will be performed in a female on each Cohort Treatment Day -1 besides the first.
[y] Electrocardiogram will be performed approximately 285 minutes after study drug administration.
[z] All medications used from 7 days prior to the Screening Visit through the Safety Visit will be recorded. If a subject spontaneously reports an adverse event after the Safety Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit, concomitant medication will be recorded.
[aa] Adverse event recording will begin after nasogastric tube placement on the first Cohort Treatment Day.
[bb] Adverse event recording will be performed on each Cohort Treatment Day -1 besides the first.
[cc] Adverse event recording will be performed before nasogastric tube placement on each Cohort Treatment Day besides the first and after nasogastric tube placement (i.e., before pretreatment buffer solution administration) on each Cohort Treatment Day.
[dd] Adverse event recording will be performed at approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report.
[ee] Spontaneously reported adverse events will be recorded after the Safety Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.
[ff] Urine samples will be obtained to test for gluten immunogenic peptides in a Group 3 subject.
[gg] Urine sample will be obtained approximately 240 minutes after study drug administration in a Group 3 subject.

Table 7. Part 3 Schedule of Assessments

Procedure	Screening Period[a]	Cohort Treatment Day -1[b]	Cohort Treatment Days[c,d]		Safety Visit[e]	Follow Up Anti-Drug Antibody Blood Sampling Visits
			Pre-Dose	Post-Dose		
Informed consent	X					
Inclusion and exclusion criteria review	X		X			
Medical history review	X	X[f]	X[g]			
Vital signs[h]	X		X[i]	X[j]	X	
Weight	X		X		X	
Height	X					
Body mass index calculation	X					
Physical examination	X		X	X[k]	X	
Randomization	X					
Intravenous catheter placement			X			
Pharmacokinetic blood sampling			X	X[l]		
Gluten-free diet confirmation		X	X			
Gastrointestinal Symptoms Questionnaire	X		X[m]	X[n]		
Nasogastric tube placement			X			
Nasogastric tube removal				X[o]		
Gastric sampling			X[p]	X[q]		
Anti-drug antibody blood sampling	X					X[r]
Clinical laboratory tests	X[s]		X[s]	X[t]	X[s]	
Pregnancy test	X[u]	X[u,v]			X[u]	
Urine drug screen	X	X			X	
Alcohol breathalyzer test	X	X			X	
Helicobacter pylori breath test	X					
Electrocardiogram	X		X	X[w]	X	
Concomitant medication review[x]	X	X	X	X	X	X
Adverse event recording[y]		X[z]	X[aa]	X[bb]	X	X[cc]
Urine sample for gluten immunogenic peptides[dd]			X	X[ee]		

[a] Screening Period of up to 4 weeks.
[b] Subject will be admitted to the Clinical Research Center the afternoon prior to each Cohort Treatment Day.
[c] Group 1 Cohorts 3A and 3B Treatment Days; Group 2 Cohorts 3C and 3D Treatment Days; Group 3 Cohorts 3E and 3F Treatment Days; Group 4 Cohorts 3G and 3H Treatment Days; Group 5 Cohorts 3I and 3J Treatment Days.
[d] Each subject will have a washout period of 3 ± 1 days between Cohort Treatment Days.
[e] Safety Visit will be performed 5 ± 2 days after the final Cohort Treatment Day, or 5 ± 2 days after the subject's last Cohort Treatment Day for a subject who withdraws early from the study.
[f] Medical history review will be performed on the first Cohort Treatment Day -1.
[g] Medical history review will be performed before nasogastric tube placement on the first Cohort Treatment Day.

[h] Vital signs will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.
[i] Vital signs will be completed before nasogastric tube placement and after nasogastric tube placement (i.e., before pretreatment buffer solution administration [Group 1], before study drug administration [Group 2, Group 4, and Group 5], or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal [Group 3]).
[j] Vital signs will be obtained approximately 70, 190, and 270 minutes after study drug administration.
[k] Complete physical examination will be performed approximately 275 minutes after study drug administration.
[l] Blood sample for pharmacokinetics will be obtained approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration.
[m] Gastrointestinal Symptoms Questionnaire will be completed before nasogastric tube placement and after nasogastric tube placement (i.e., before pretreatment buffer solution administration [Group 1], before study drug administration [Group 2, Group 4 and Group 5], or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal [Group 3]).
[n] Gastrointestinal Symptoms Questionnaire will be completed approximately 30, 130, and 325 minutes (Group 1, Group 2, Group 3 and Group 5 subject) or 130 and 325 minutes (Group 4 subject) after study drug administration.
[o] Nasogastric tube will be removed approximately 80 minutes after study drug administration.
[p] Gastric sample (approximately 5 mL) will be obtained after nasogastric tube placement for pH testing (to confirm tube placement and serve as pretreatment pH measurement) and gluten quantification.
[q] Gastric sample (approximately 15 mL) will be obtained 35 minutes after study drug administration in a Group 1, Group 2, Group 3, and Group 5 subject, and gastric sample (entire gastric content) will be obtained 65 minutes after study drug administration in a Group 1, Group 2, Group 3, Group 4, and Group 5 subject, for pH testing and gluten quantification. The aspirated volume of the approximately 15 mL gastric sample obtained 35 minutes after study drug administration and the entire gastric content sample obtained 65 minutes after study drug administration will be measured before a portion is removed for pH testing and gluten quantification.
[r] Blood sample for anti-drug antibody testing will be obtained 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day. In a subject who develops anti-drug antibodies, the anti-drug antibody level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first.
[s] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained in the 12-hour fasting state (water will be allowed during the 12-hour period before the Screening and Safety Visit clinical laboratory tests, but not during the 12-hour period before the Cohort Treatment Day pre-dose clinical laboratory tests).
[t] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained approximately 240 minutes after study drug administration; urinalysis may be done at later time point (up to 480 minutes after study drug administration), if necessary.
[u] Serum pregnancy test will be performed in a female at Screening, on the first Cohort Treatment Day -1, and at the Safety Visit.
[v] Urine pregnancy test will be performed in a female on the second Cohort Treatment Day -1.
[w] Electrocardiogram will be performed approximately 285 minutes after study drug administration.
[x] All medications used from 7 days prior to the Screening Visit through the Safety Visit will be recorded. If a subject spontaneously reports an adverse event after the Safety Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit, concomitant medication will be recorded.
[y] Adverse event recording will begin after nasogastric tube placement on the first Cohort Treatment Day.
[z] Adverse event recording will be performed on the second Cohort Treatment Day -1.
[aa] Adverse event recording will be performed before nasogastric tube placement on the second Cohort Treatment Day and after nasogastric tube placement (i.e., before pretreatment buffer solution administration [Group 1], before study drug administration [Group 2, Group 4, and Group 5], or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal [Group 3]) on each Cohort Treatment Day.
[bb] Adverse event recording will be performed at approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report.
[cc] Spontaneously reported adverse events will be recorded after the Safety Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.
[dd] Urine samples will be obtained to test for gluten immunogenic peptides.
[ee] Urine sample will be obtained approximately 240 minutes after study drug administration.

Table 8. Part 4 Schedule of Assessments

Procedure	Screening Period[a]	Cohort Treatment Periods[c,d]						Safety Visit[e]	Follow Up Anti-Drug Antibody Blood Sampling Visits
		Day -1[b]	Day 1		Day 4	Day 5			
			Pre-dose	Post-dose		Pre-dose	Post-dose		
Informed consent	X								
Inclusion and exclusion criteria review	X		X			X			
Medical history review	X	X[f]	X[g]						
Vital signs[h]	X		X	X[i]		X		X	
Weight	X		X			X		X	
Height	X								
Body mass index calculation	X								
Physical examination	X		X	X[j]		X		X	
Randomization	X								
Intravenous catheter placement			X			X			
Pharmacokinetic blood sampling			X	X[k]		X	X[k]		
Dispense PvP003 and Daily PvP003 Dosing Diary				X					
PvP003 return inventory and Daily PvP003 Dosing Diary review					X				
Dispense Gastrointestinal Symptoms Questionnaires				X[l]					
Gastrointestinal Symptoms Questionnaires review, collection, and reminders		X[m]			X[m]				
Gastrointestinal Symptoms Questionnaires collection								X	
Gastrointestinal Symptoms Questionnaire	X		X	X[n]		X			
Gluten-free or reduced gluten diet question	X[o]		X[p]			X[p]			
Anti-drug antibody blood sampling	X								X[q]
Clinical laboratory tests	X[r]		X[r]	X[s]		X[r]		X[r]	
Pregnancy test	X[t]	X[t,u]						X[t]	
Urine drug screen	X	X			X			X	
Alcohol breathalyzer test	X	X			X			X	
Helicobacter pylori breath test	X								
Electrocardiogram	X		X	X[v]		X		X	
Concomitant medication review[w]	X	X	X	X	X	X	X	X	
Adverse event recording[x]		X[y]	X[z]	X[aa]	X	X	X	X	X[bb]
Urine sample for gluten immunogenic peptides[cc]			X			X			

[a] Screening Period of up to 4 weeks.
[b] Subject will be admitted to the Clinical Research Center the afternoon prior to Day 1 and Day 5 of each Cohort Treatment Period.
[c] Cohorts 4A and 4B Treatment Periods; each Cohort Treatment Period will be 5 days, but may be extended by 1 day.
[d] Each subject will have a washout period of 3 ± 1 days between Day 5 of the first Cohort Treatment Period and Day 1 of the second Cohort Treatment Period.
[e] Safety Visit will be performed 5 ± 2 days after Day 5 of the second Cohort Treatment Period, or 5 ± 2 days after the subject's last dose of study drug for a subject who withdraws early from the study.
[f] Medical history review will be performed on Day -1 of the first Cohort Treatment Period.
[g] Medical history review will be performed before administration of the first daily dose of study drug on Day 1 of the first Cohort Treatment Period.
[h] Vital signs will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.
[i] Vital signs will be obtained approximately 70 and 190 minutes after administration of the first daily dose of study drug on Day 1 of each Cohort Treatment Period.
[j] Complete physical examination will be performed approximately 215 minutes after administration of the first daily dose of study drug on Day 1 of each Cohort Treatment Period.
[k] Blood sample for pharmacokinetics will be obtained approximately 15, 30, 45, 60, 120, 180, and 240 minutes after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period.
[l] Gastrointestinal Symptoms Questionnaires will be dispensed to the subject on Day 1 of the first Cohort Treatment Period for the subject to complete every day at bedtime through the day prior to the Safety Visit.
[m] Gastrointestinal Symptoms Questionnaires dispensed to the subject on Day 1 of the first Cohort Treatment Period will be reviewed on Day -1 of the second Cohort Treatment Period and Day 4 of each Cohort Treatment Period to ensure that the subject is completing them every day, completed Gastrointestinal Symptoms Questionnaires will be collected, and the subject will be reminded to complete the Gastrointestinal Symptoms Questionnaire every day at bedtime through the day prior to the Safety Visit and to bring them to each visit through the Safety Visit.
[n] Gastrointestinal Symptoms Questionnaire will be completed approximately 50 and 130 minutes after administration of the first daily dose of study drug on Day 1 of each Cohort Treatment Period.
[o] Subject will be asked "Do you generally follow a gluten-free or reduced gluten diet?" and the answer will be recorded as "yes" or "no."
[p] Subject will be asked "Did you generally follow a gluten-free or reduced gluten diet in the past 24 hours?" and the answer will be recorded as "yes" or "no."
[q] Blood sample for anti-drug antibody testing will be obtained 14 ± 2 days and 28 ± 2 days after Day 5 of the second Cohort Treatment Period. In a subject who develops anti-drug antibodies, the anti-drug antibody level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever comes first.
[r] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained in the 12-hour fasting state (water will be allowed).
[s] Clinical laboratory tests (chemistry, hematology, and urinalysis) will be obtained approximately 240 minutes after administration of the first daily dose of study drug on Day 1 of each Cohort Treatment Period.
[t] Serum pregnancy test will be performed in a female at Screening, on Day -1 of the first Cohort Treatment Period, and at the Safety Visit.
[u] Urine pregnancy test will be performed in a female on Day -1 of the second Cohort Treatment Period.
[v] Electrocardiogram will be performed approximately 225 minutes after administration of the first daily dose of study drug on Day 1 of each Cohort Treatment Period.
[w] All medications used from 7 days prior to the Screening Visit through the Safety Visit will be recorded. If a subject spontaneously reports an adverse event after the Safety Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit, concomitant medication will be recorded.
[x] Adverse event recording will begin after administration of the first daily dose of study drug on Day 1 of the first Cohort Treatment Period.
[y] Adverse event recording will be performed on Day -1 of the second Cohort Treatment Period.
[z] Adverse event recording will be performed before administration of the first daily dose of study drug on Day 1 of the second Cohort Treatment Period.
[aa] Adverse event recording will be performed at approximately 40, 125, and 180 minutes after administration of the first daily dose of study drug, and at any other time upon spontaneous subject report, on Day 1 of each Cohort Treatment Period.
[bb] Spontaneously reported adverse events will be recorded after the Safety Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.
[cc] Urine samples will be obtained to test for gluten immunogenic peptides.

5 RANDOMIZATION AND BLINDING

5.1 Randomization

Part 1

Part 1 of this study is non-randomized.

Part 2

Each Group 1 subject will receive three treatments, but will be randomized to one of six possible treatment orders. Subjects will be randomized to treatment order in a 1:1:1:1:1:1 ratio.

- Cohort 2A, Cohort 2B, Cohort 2C
- Cohort 2A, Cohort 2C, Cohort 2B
- Cohort 2B, Cohort 2C, Cohort 2A
- Cohort 2B, Cohort 2A, Cohort 2C
- Cohort 2C, Cohort 2A, Cohort 2B
- Cohort 2C, Cohort 2B, Cohort 2A

Each Group 2 subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 2D, Cohort 2E
- Cohort 2E, Cohort 2D

Each Group 3 subject will be randomized to a 1 g gluten-containing study meal or a 6 g gluten-containing study meal in a 2:1 ratio, respectively, and to PvP001 dose and treatment order in a 1:1 ratio. A subject randomized to receive the 1 g gluten-containing study meal will receive both PvP001 placebo and PvP001 300 mg in one of two possible treatment orders or will receive both PvP001 placebo and PvP001 600 mg in one of two possible treatment orders. Each subject randomized to receive the 6 g gluten-containing study meal will receive both PvP001 placebo and PvP001 900 mg in one of two possible treatment orders.

- Cohort 2F, Cohort 2G
- Cohort 2G, Cohort 2F
- Cohort 2F, Cohort 2H
- Cohort 2H, Cohort 2F
- Cohort 2I, Cohort 2J
- Cohort 2J, Cohort 2I

Part 3

Each Group 1 subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 3A, Cohort 3B
- Cohort 3B, Cohort 3A

Each Group 2 subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 3C, Cohort 3D
- Cohort 3D, Cohort 3C

Each Group 3 subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 3E, Cohort 3F
- Cohort 3F, Cohort 3E

Each Group 4 subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 3G, Cohort 3H
- Cohort 3H, Cohort 3G

Each Group 5 subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 3I, Cohort 3J
- Cohort 3J, Cohort 3I

Part 4

Each subject will receive two treatments, but will be randomized to one of two possible treatment orders. Subjects will be randomized to treatment order in a 1:1 ratio.

- Cohort 4A, Cohort 4B
- Cohort 4B, Cohort 4A

Randomization will occur only after the subject has been determined to be eligible for study participation based on the inclusion and exclusion criteria. The randomization schedule will be generated using a computer program and verified for accuracy using strict quality control procedures. Prior to each eligible subject's participation in the first Cohort Treatment Day, the next unique, sequentially available randomization number will be assigned to the subject using

an interactive web response system. The randomization number will be entered into the Case Report Form (CRF).

5.2 Blinding

Part 1

Treatment will be single-blind (i.e., each subject will be blinded to the PvP001 and PvP002 dose [PvP001 placebo, PvP001 100 mg, PvP001 300 mg, PvP001 900 mg, or MFD of PvP002]).

Part 2

Treatment will be single-blind (i.e., a Group 1 subject will be blinded to the PvP001 dose [placebo or the MTD], a Group 2 subject will be blinded to which PvP002 treatment [comparator {sterile water} or the MFD] is active study drug, and a Group 3 subject will be blinded to the PvP001 dose [placebo, 300 mg, 600 mg, or 900 mg]). A Group 3 subject will also be blinded to the amount of gluten in the study meal.

Part 3

Treatment will be single-blind (i.e., each subject will be blinded to which PvP003 treatment [placebo, 150 mg, or 600 mg] is active study drug). A Group 4 subject will also be blinded to which of the two study meals is gluten-free and contains no Miralax and which of the two study meals contains gluten and Miralax.

Part 4

Treatment will be single-blind (i.e., each subject will be blinded to which PvP003 treatment [placebo or 600 mg] is active study drug).

6 STUDY POPULATION SELECTION

6.1 Study Population

The study population will consist of healthy adults 18-59 years of age, inclusive, and adults with CeD 18-64 years of age, inclusive. Study entry criteria will be men or women with no significant medical disease (i.e., healthy volunteers in Part 1, Part 2, Part 3, and Part 4) or with well controlled CeD (i.e., patients with CeD in Part 1).

Section 6.2 and Section 6.3 contain a complete list of inclusion criteria and exclusion criteria, respectively.

6.2 Inclusion Criteria

A subject must meet all the following criteria to be eligible to participate in the study:

Part 1, Part 2, Part 3, and Part 4

1. Male or female age 18- 59 years, inclusive, for healthy volunteers (Part 1, Part 2, Part 3, and Part 4); male or female age 18-64 years, inclusive, for patients with CeD (Part 1)
2. Body mass index <35 kg/m^2
3. Absence of clinically relevant gastrointestinal symptoms and signs as indicated by medical history, GSQ, and physical examination at Screening; medical history review/AE recording on Cohort Treatment Day -1, and medical history review/AE recording, GSQ, and physical examination at the beginning of the Cohort Treatment Day, in a Part 1, Part 2, and Part 3 subject; and medical history review/AE recording on Day -1 and Day 4, and medical history review/AE recording, GSQ, and physical examination at the beginning of Day 1, of the Cohort Treatment Period in a Part 4 subject
4. Able to abstain from alcohol for 72 hours prior to the Screening Visit; for 72 hours prior to and after the Cohort Treatment Day (Part 1, Part 2, and Part 3); for 72 hours prior to the Safety Visit (Part 2 and Part 3); and for 72 hours prior to Day 1 of the first Cohort Treatment Period through the Safety Visit (Part 4)
5. A female subject must have a negative pregnancy test at Screening and on Cohort Treatment Day -1 (Part 1, Part 2, and Part 3) or a negative pregnancy test at Screening and on Day -1 of each Cohort Treatment Period (Part 4), and must agree to continue acceptable birth control measures (e.g., abstinence, a stable hormonal contraceptive, double-barrier method, or vasectomy in partner) from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
6. A male subject must agree to continue acceptable birth control measures (e.g., abstinence, latex condom, or vasectomy), or must have a female partner who will continue acceptable birth control measures (e.g., abstinence, a stable hormonal contraceptive, or double-barrier method), from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit

7. Able to read and understand English
8. Able to provide written informed consent

Additional Inclusion Criteria for Part 1, Part 2, Part 3, and Part 4 Healthy Adult Volunteers

9. No current, recent (within 7 days prior to the Screening Visit), or planned (from the Screening Visit through the Safety Follow Up Call [Part 1] or Safety Visit [Part 2, Part 3, and Part 4]) use of over-the-counter or prescription medication via any route of administration. This includes, but is not limited to, aspirin and other nonsteroidal anti-inflammatory drugs (which may affect gastrointestinal permeability), gastric acid suppressive medications, vitamins, minerals, and herbal products. Occasional, as needed use of an over-the-counter medication during this time may be acceptable, provided it is approved by the Investigator and Medical Monitor. The exceptions are a hormonal contraceptive for birth control, provided it has been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit; the per protocol use of topical lidocaine, Miralax, and ondansetron on the Cohort Treatment Days (Part 2 and Part 3); and the per protocol use of Nexium before the Cohort 2C Treatment Day (Part 2 Group 1).
10. No significant medical disease, clinical laboratory evidence of significant medical disease, or significant ECG abnormality per the Investigator's assessment
11. No history of upper or lower gastrointestinal tract disease, disorder, or symptoms; this includes, but is not limited to, gastroesophageal reflux disease, esophageal disease, swallowing disorder, ulcer, abnormal gastric emptying, *Helicobacter pylori* infection, gastrointestinal surgery, irritable bowel syndrome, or CeD
12. No history of intolerance, hypersensitivity, or idiosyncratic reaction to gluten or to any food or food ingredient (including a carbohydrate [e.g., lactose], polyol, additive, or preservative), including a food or food ingredient in the study meal
13. Able to maintain a GFD for 24 hours prior to the Cohort Treatment Day (Part 1, Part 2, and Part 3), or usually ingests meals TID (i.e., breakfast, lunch, and dinner) and is able to continue doing so during each Cohort Treatment Period (Part 4)

Additional Inclusion Criteria for Part 1 Patients with Celiac Disease

14. Documented history of CeD, defined as a history (at the time of diagnosis) of duodenal biopsy findings consistent with active CeD per the patient's medical chart note or pathology report, or of serum tissue transglutaminase immunoglobulin A (tTG IgA) antibodies, deamidated gliadin peptide immunoglobulin A or immunoglobulin G (DGP IgA or DGP IgG) antibodies, or endomysial immunoglobulin A or immunoglobulin G (EMA IgA or EMA IgG) antibodies, ≥5 times the upper limit of normal per the patient's medical chart note or laboratory report
15. CeD is well controlled, defined as compliance with a GFD and resolution of chronic symptoms for ≥6 months prior to the Screening Visit; occasional accidental gluten exposure, if it occurred during the 6 months prior to the Screening Visit, should not have resulted in severe symptoms or symptoms lasting >48 hours

16. No history of severe CeD symptoms, defined as symptoms resulting in the inability to perform usual daily activities with gluten exposure, severe gluten-related neurologic symptoms (e.g., ataxia, peripheral neuropathy), or significant gastrointestinal or systemic complications of CeD
17. Serum tTG IgA antibodies ≤1.5 times the upper limit of normal and a normal total IgA at Screening
18. Asthma, allergic rhinitis, or hypothyroidism, if present, must be well controlled and stable for ≥3 months prior to the Screening Visit
19. No other significant medical disease, clinical laboratory evidence of other significant medical disease, or significant ECG abnormality per the Investigator's assessment
20. No current, recent (within 7 days prior to the Screening Visit), or planned (from the Screening Visit through the Safety Follow Up Call) use of aspirin and other nonsteroidal anti-inflammatory drugs (which may affect gastrointestinal permeability), proton pump inhibitors, and herbal products. Occasional, as needed use of an over-the-counter medication during this time may be acceptable, provided it is approved by the Investigator and Medical Monitor. Other acceptable medications are a hormonal contraceptive for birth control, inhaled medication for asthma, oral and intranasal medication for allergic rhinitis, thyroid hormone for hypothyroidism, and other medication that the Investigator and Medical Monitor determine will not compromise the safety of the subject or interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments), provided they have been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.
21. No current active irritable bowel syndrome, no history of abnormal gastric emptying, and, based on the Investigator's assessment, no history of other significant upper or lower gastrointestinal tract disease, disorder, symptoms, or surgery. Current gastroesophageal reflux symptoms or disease which is being treated regularly with an H_2-receptor antagonist or an antacid at the same dose and frequency for ≥1 month prior to the Screening Visit, and which is stable, defined as no symptoms for ≥1 month prior to the Screening Visit, may be acceptable, provided this is approved by the Investigator and will not compromise the safety of the subject or interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments), and the medication can be discontinued 48 hours prior to the Cohort Treatment Day through the 24-Hour Safety Assessment with no expected symptoms, compromise of subject safety, or interference with or complication of study procedures or assessments (including gastrointestinal symptom or sign assessments) during this period of discontinuation.
22. No history of intolerance, hypersensitivity, or idiosyncratic reaction to any other food or food ingredient (including a carbohydrate [e.g., lactose], polyol, additive, or preservative), including a food or food ingredient in the study meal
23. Able to continue a GFD from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit

6.3 Exclusion Criteria

A subject who meets any of the following criteria will be excluded from participating in the study:

Part 1, Part 2, Part 3, and Part 4

1. Any condition or abnormality (including clinical laboratory, ECG, physical examination, or vital sign abnormalities), current or past, that, in the opinion of the Investigator or Medical Monitor, would compromise the safety of the subject, or would interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments). Such conditions include or may include psychiatric, neurologic/neuromuscular, developmental, cardiovascular, renal, immunologic (including autoimmune), infectious, hematologic (including clotting or bleeding disorder), metabolic, otolaryngologic, or pulmonary disease or disorder. These and any other significant medical history should be discussed with the Medical Monitor prior to subject enrollment.
2. Current symptoms or signs of acute illness
3. Chronic viral infection or immunodeficiency condition
4. Any female who is pregnant, planning to become pregnant during the study, or breast-feeding; any male who is planning to father a child during the study
5. History of intolerance, hypersensitivity, or idiosyncratic reaction to any of the ingredients in PvP001, PvP002, PvP003, PvP003 placebo, or the CCI [redacted] pretreatment buffer solution
6. History of intolerance, hypersensitivity, or idiosyncratic reaction to an aminoglycoside
7. Receipt (or planned receipt) of an investigational medication within 4 weeks prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
8. Alcohol consumption >5 drinks/week, alcohol consumption within 72 hours prior to any study visit (Part 1, Part 2, and Part 3), alcohol consumption within 72 hours prior to Day 1 of the first Cohort Treatment Period through the Safety Visit (Part 4), or a positive alcohol breathalyzer test at any study visit
9. History of illicit or recreational drug use within the three years prior to the Screening Visit, or a positive urine drug screen at any study visit
10. Positive *Helicobacter pylori* breath test at Screening
11. Use of tobacco or nicotine products, including smoking, smokeless tobacco, e-cigarettes, or nicotine replacement products within 12 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit
12. History or high risk of noncompliance with treatment or clinic visits

Additional Exclusion Criteria for Part 2 and Part 3

13. History of intolerance, hypersensitivity, or idiosyncratic reaction to lidocaine (or other ingredients in the topical lidocaine preparation) or other local anesthetics, Nexium (or other ingredients in the capsule) or other PPIs, polyethylene glycol (PEG), or ondansetron (or other

ingredients in the injectable ondansetron preparation) or other serotonin 5-HT_3 receptor antagonists

14. For a Part 2 and Part 3 subject in whom an NG tube will be placed, history of upper respiratory tract trauma or surgery, mid-face trauma, or skull base fracture; current or history of septal perforation, ulceration, or erosion, nasal or sinus polyps, sinus disease, or severe nasal bleeding; current septal deviation, nasal obstruction or congestion, or noninfectious rhinitis that, in the opinion of the Investigator or Medical Monitor, would compromise the safety of the subject. (For a Part 2 and Part 3 subject in whom an orogastric [OG] tube will be placed, current or history of oropharyngeal or dental signs, symptoms, or disease that, in the opinion of the Investigator or Medical Monitor, would compromise the safety of the subject, or current loose tooth.)

6.4 Eligibility Questions

For questions about subject eligibility, including inclusion and exclusion criteria, contact the Medical Monitor and designee:

PPD

7 STUDY CONDUCT

7.1 Subject Identification

At the Screening Visit, each subject will be assigned a unique number after the Informed Consent Form (ICF) is signed. The subject's number and initials will identify each subject throughout the study.

7.2 Study Procedures by Time Point

On the Cohort Treatment Day, procedures with protocol-specified time points that are within the first hour after study drug administration will occur within ± 5 minutes of the designated time points and procedures with protocol-specified time points beyond the first hour after study drug administration will occur within ± 15 minutes of the designated time points. The exceptions are:

- Aspiration of the entire gastric content must begin 35-40 minutes after study drug administration (i.e., it should begin 35 minutes after study drug administration, but may begin, at most, 40 minutes after study drug administration) in a Part 2 Group 1 and Part 2 Group 2 subject
- Aspiration of gastric contents from the NG tube, followed by reinjection through the NG tube, will occur within ± 1 minute of the designated time points, which are 10, 12, and 14 minutes after study drug administration, in a Part 2 Group 3, Part 3 Group 3, and Part 3 Group 4 subject
- Aspiration of the 5 mL gastric sample must begin 20-25 minutes after study drug administration (i.e., it should begin 20 minutes after study drug administration, but may begin, at most, 25 minutes after study drug administration) in a Part 2 Group 3 subject. Aspiration of the 5 mL gastric sample must begin 35-40 minutes after study drug administration (i.e., it should begin 35 minutes after study drug administration, but may begin, at most, 40 minutes after study drug administration) in a Part 2 Group 3 subject
- Aspiration of the 15 mL gastric sample must begin 35-40 minutes after study drug administration (i.e., it should begin 35 minutes after study drug administration, but may begin, at most, 40 minutes after study drug administration) in a Part 3 Group 1, Part 3 Group 2, Part 3 Group 3, and Part 3 Group 5 subject
- Aspiration of the entire gastric content must begin 65-70 minutes after study drug administration (i.e., it should begin 65 minutes after study drug administration, but may begin, at most, 70 minutes after study drug administration) in a Part 2 Group 3, Part 3 Group 1, Part 3 Group 2, Part 3 Group 3, Part 3 Group 4, and Part 3 Group 5 subject
- Ingestion of the 1 g gluten-containing study meal must begin 30-35 minutes after study drug administration (i.e., it should begin 30 minutes after study drug administration, but may begin, at most, 35 minutes after study drug administration) in a Part 3 Group 4 subject
- The 240-minute post-dose urine sample for gluten immunogenic peptides should be obtained prior to the ingestion of food and liquids (normal diet) ad libitum in a Part 2

Group 3, Part 3 Group 1, Part 3 Group 2, Part 3 Group 3, Part 3 Group 4, and Part 3 Group 5 subject

The 24-Hour Safety Assessment procedures will occur 24 ± 1 hours after study drug administration in a Part 1 subject.

In a Part 4 subject, either 5-day Cohort Treatment Period, or both, may be extended by 1 day if necessary (e.g., for scheduling or administrative purposes). In this case, the subject will be admitted to the Clinical Research Center the afternoon prior to Day 6 of the Cohort Treatment Period (i.e., in the afternoon on Day 5 of the 6-day Cohort Treatment Period).

7.2.1 Screening Visit/Screening Period (Part 1, Part 2, Part 3, and Part 4)

At the Screening Visit, the potential subject will receive an explanation of the purpose and nature of the study and will be asked to review and sign the ICF prior to any study-related procedures. Screening procedures will be performed after informed consent is obtained, but they do not all need to be completed on the same day. The subject will be fasting (nothing by mouth except water) for at least 12 hours prior to the Screening clinical laboratory tests. The Screening Period will be up to 4 weeks to allow for all the following Screening procedures to be performed and for subject scheduling:

- Medical history review
- GSQ
- Concomitant medication review
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Height
- BMI calculation
- Complete physical examination
- ECG
- Blood sampling for ADA
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Serum tTG IgA antibodies and total IgA (patient with CeD)
- Serum pregnancy test (in female)
- Urine drug screen
- Alcohol breathalyzer test
- *Helicobacter pylori* breath test

- Ask a Part 4 subject: "Do you generally follow a gluten-free or reduced gluten diet?" and record the answer as "yes" or "no"
- Review inclusion and exclusion criteria and determine eligibility for study participation after completion and review of results of all Screening procedures
- Randomize Part 2, Part 3, and Part 4 subject once Screening is completed and subject meets eligibility criteria
- Dispense Nexium to Part 2 Group 1 subject randomized to Cohort 2C first and train subject on dosing and completion of the Daily Nexium Dosing Diary
- Remind subject of study restrictions as noted in Section 10

7.2.1.1 Re-screening Procedures

Re-screening may be allowed in certain circumstances (e.g., recent minor illness), but requires documented permission from the Medical Monitor. If a subject is re-screened, the subject will receive a new subject number.

A subject who is determined to be eligible for the study at Screening but is unable to participate in the study within the 4-week Screening Period for administrative reasons may be considered for future participation without re-screening (e.g., enrollment of subjects in the intended Cohort has been completed, but enrollment of subjects in the next Cohort will soon begin) at the discretion of the Medical Monitor, provided the subject continues to meet the eligibility criteria. The Medical Monitor may request that certain Screening procedures be repeated before proceeding with enrollment.

7.2.1.2 Screening Failures

Any subject who does not meet the eligibility criteria will be considered a Screening failure. The reason for Screen failure will be documented.

7.2.2 Cohort Treatment Day -1 (Part 1)

Admission to the Clinical Research Center on the day prior to the Cohort Treatment Day will occur within 4 weeks of the Screening Visit.

The subject will report to the Clinical Research Center the afternoon prior to the Cohort Treatment Day, will eat a gluten-free dinner at the Clinical Research Center, and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

At check in, the following procedures will be performed:

- Serum pregnancy test (in female), urine drug screen, and alcohol breathalyzer test
  - Results must be reviewed on Cohort Treatment Day -1
    - If any of these tests is positive, the subject will be withdrawn from the study
- Medical history review

- Concomitant medication review
- If applicable, confirm discontinuation of an H_2-receptor antagonist or antacid beginning 48 hours before the Cohort Treatment Day in a patient with CeD
- Confirm ingestion of a GFD beginning the morning of Cohort Treatment Day -1 in a healthy volunteer or continuation of the GFD since the Screening Visit in a patient with CeD

7.2.3 Cohort Treatment Day Pre-Dose (Part 1)

On the Cohort Treatment Day, the following procedures will be performed prior to pretreatment buffer solution administration:

- Medical history review
- GSQ
- Concomitant medication review
- If applicable, confirm discontinuation of an H_2-receptor antagonist or antacid beginning 48 hours before the Cohort Treatment Day in a patient with CeD; if applicable, confirm withholding of the morning and/or afternoon dose(s) of other permitted concomitant medication on the Cohort Treatment Day in a patient with CeD
- Confirm ingestion of a GFD for 24 hours in a healthy volunteer or continuation of the GFD since the Screening Visit in a patient with CeD
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Complete physical examination
- ECG
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Inclusion and exclusion criteria review
- Intravenous (IV) catheter placement
- Blood sampling for PK immediately prior to pretreatment buffer solution administration (pre-dose [time 0])

After completion of all the above study procedures, the pretreatment buffer solution will be administered orally. Immediately after pretreatment buffer solution administration, study drug will be administered orally. Immediately after study drug administration, a standardized gluten-free study meal will be ingested; ingestion of the entire study meal should be completed within 10 minutes of study drug administration.

7.2.4 Cohort Treatment Day Post-Dose (Part 1)

After pretreatment buffer solution administration, study drug administration, and study meal ingestion have all been completed, the following procedures will be performed:

- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration
- AE recording approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report
- GSQ approximately 30, 130, and 325 minutes after study drug administration
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70, 190, and 270 minutes after study drug administration
- Clinical laboratory blood tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration (urinalysis may be done at a later time point [up to 480 minutes after study drug administration] if necessary)
- Complete physical examination approximately 275 minutes after study drug administration
- ECG approximately 285 minutes after study drug administration
- Ice chips (a maximum of 240 mL up to every hour) may be ingested beginning one hour after study drug administration and continuing until ad libitum ingestion of food and liquids begins
- Ingestion of food and liquids (normal diet in a healthy subject and GFD in a patient with CeD) ad libitum may begin approximately 185 minutes after study drug administration (i.e., after completion of the 180-minute post-dose AE recording), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator
- Concomitant medication review
- The subject will remain in the Clinical Research Center until the 24-Hour Safety Assessment is completed approximately 24 hours after study drug administration
- The subject will begin an overnight fast (nothing by mouth except water for at least 12 hours) the evening prior to the 24-Hour Safety Assessment
- The IV catheter may be removed after the final post-dose blood samples are drawn on the Cohort Treatment Day or may remain in place to obtain blood samples for the 24-Hour Safety Assessment

7.2.5 24-Hour Safety Assessment (Part 1)

The 24-Hour Safety Assessment will be conducted approximately 24 hours after study drug administration. For a subject who withdraws from the study before receiving study drug (i.e., PvP001, PvP001 placebo, or PvP002), a 24-Hour Safety Assessment will not be conducted.

The subject will be fasting (nothing by mouth except water) for at least 12 hours prior to the 24-Hour Safety Assessment. The following procedures will be performed:

- AE recording
- GSQ
- Concomitant medication review
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Complete physical examination
- ECG
- Blood sampling for PK
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- If the IV catheter is still in place, it will be removed after the final blood samples have been obtained
- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition
- Remind subject of study restrictions as noted in Section 10

7.2.6 Safety Follow Up Call (Part 1)

A Safety Follow Up Call will occur for each subject 5 ± 2 days after the 24-Hour Safety Assessment for AE recording and concomitant medication review. At the discretion of the Investigator, the subject will return to the Clinical Research Center for a safety follow up visit and/or a safety follow up procedure(s) (e.g., clinical laboratory tests). For a subject who withdraws from the study before receiving study drug (i.e., PvP001, PvP001 placebo, or PvP002), a Safety Follow Up Call will not occur.

7.2.7 Follow Up Anti-Drug Antibody Blood Sampling Visits (Part 1)

Each subject will return to the Clinical Research Center for blood sampling for ADA testing 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day, unless the subject withdraws from the study before receiving study drug (i.e., PvP001, PvP001 placebo, or PvP002).

7.2.8 Cohort Treatment Days -1 (Part 2)

Admission to the Clinical Research Center on the day prior to the first Cohort Treatment Day will occur within 4 weeks of the Screening Visit.

The subject will report to the Clinical Research Center the afternoon prior to each of three Cohort Treatment Days for a Group 1 subject or prior to each of two Cohort Treatment Days for a Group 2 or Group 3 subject, will eat a gluten-free dinner at the Clinical Research Center, and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

At check in, the following procedures will be performed:

- Serum (first Cohort Treatment Day) or urine (all other Cohort Treatment Days) pregnancy test (in female), urine drug screen, and alcohol breathalyzer test
  - Results must be reviewed on Cohort Treatment Day -1
    - If the pregnancy test or urine drug screen is positive, the subject will be withdrawn from the study
    - If the alcohol breathalyzer test is positive, the visit may be rescheduled at the discretion of, and if approved by, the Investigator and Medical Monitor
- Medical history (first Cohort Treatment Day) review or AE (all other Cohort Treatment Days) recording
- Concomitant medication review
- Confirm ingestion of a GFD beginning the morning of Cohort Treatment Day -1
- On Cohort 2C Treatment Day -1, assess compliance with the Nexium pretreatment regimen using the subject's Daily Nexium Dosing Diary and an inventory of the subject's returned Nexium capsules. The final dose (dose 7) of Nexium will be administered to the subject by the Clinical Research Center personnel at bedtime the night before the Cohort 2C Treatment Day.

7.2.9 Cohort Treatment Days Pre-Dose (Part 2)

On the Cohort Treatment Day, the following procedures will be performed prior to NG tube placement:

- Confirm fasting status (nothing by mouth for at least 12 hours)
- Medical history (first Cohort Treatment Day) review or AE (all other Cohort Treatment Days) recording
- GSQ
- Concomitant medication review
- Confirm ingestion of a GFD for 24 hours
- Vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Complete physical examination

- ECG
- IV catheter placement
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Urine sample for gluten immunogenic peptides (in Group 3 subject)
- Inclusion and exclusion criteria review

On the Cohort Treatment Day, the following procedures will be performed prior to pretreatment buffer solution administration:

- NG tube placement with auscultation and gastric sampling (approximately 5 mL) for pH testing (to confirm NG tube placement and serve as the pretreatment pH measurement) and gluten quantification
- AE recording after NG tube placement
- GSQ after at least an approximately 15-minute waiting period following NG tube placement, or after a longer waiting period when any signs or symptoms that occur in association with the NG tube placement procedure, if applicable, have resolved or are considered non-severe and stable by the Investigator
- Vital signs after at least an approximately 15-minute waiting period following NG tube placement, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Blood sampling for PK immediately prior to pretreatment buffer solution administration (pre-dose [time 0])

After completion of all the above study procedures, the pretreatment buffer solution will be administered orally. Immediately after pretreatment buffer solution administration, study drug will be administered orally. Immediately after study drug administration, a standardized gluten-containing study meal will be ingested; ingestion of the entire study meal should be completed within 10 minutes of study drug administration.

7.2.10 Cohort Treatment Days Post-Dose (Part 2)

After pretreatment buffer solution administration, study drug administration, and study meal ingestion have all been completed, the following procedures will be performed in a Group 1 and Group 2 subject:

- Ask the subject to move approximately 10 minutes after study drug administration
- Aspiration of approximately 30-40 mL of gastric contents from the NG tube, followed by reinjection through the NG tube, using a 60 mL syringe approximately 10, 15, and 20 minutes after study drug administration
- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration
- AE recording approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report

- GSQ approximately 30, 130, and 325 minutes after study drug administration
- Gastric sampling (entire gastric content) for pH testing and gluten quantification 35 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 35 minutes after study drug administration.) The aspirated volume of the entire gastric content sample will be measured before a portion is removed for pH testing and gluten quantification.
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70, 190, and 270 minutes after study drug administration
- Clinical laboratory tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration (urinalysis may be done at a later time point [up to 480 minutes after study drug administration] if necessary)
- Complete physical examination approximately 275 minutes after study drug administration
- ECG approximately 285 minutes after study drug administration
- NG tube removal approximately 135 minutes after study drug administration (i.e., after completion of the 125-minute post-dose AE recording and 130-minute post-dose GSQ)
- Ingestion of food and liquids (normal diet) ad libitum may begin approximately 185 minutes after study drug administration (i.e, after completion of the 180-minute post-dose AE recording), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. (Note: The NG tube will have been removed prior to the ingestion of food and liquids [normal diet] ad libitum.)
- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review
- Dispense Nexium to Part 2 Group 1 subject who will participate in Cohort 2C at the next visit and train subject on dosing and completion of the Daily Nexium Dosing Diary
- Remind subject of study restrictions as noted in Section 10
- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

After pretreatment buffer solution administration, study drug administration, and study meal ingestion have all been completed, the following procedures will be performed in a Group 3 subject:

- Ask the subject to move approximately 10 and 45 minutes after study drug administration
- Aspiration of approximately 30-40 mL of gastric contents from the NG tube, followed by reinjection through the NG tube, using a 60 mL syringe 10, 12, and 14 minutes after study drug administration
- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration
- Gastric sampling for pH testing and gluten quantification

  - Gastric sampling (approximately 5 mL) 20 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 20 minutes after study drug administration.)
  - Gastric sampling (approximately 5 mL) 35 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 35 minutes after study drug administration.)
  - Gastric sampling (entire gastric content) 65 minutes after study drug administration. (Note: it is important to begin gastric sample aspiration 65 minutes after study drug administration.) The aspirated volume of the entire gastric content sample will be measured before a portion is removed for pH testing and gluten quantification.
- AE recording approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report
- GSQ approximately 30, 130, and 325 minutes after study drug administration
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70, 190, and 270 minutes after study drug administration
- Clinical laboratory tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration (urinalysis may be done at a later time point [up to 480 minutes after study drug administration] if necessary)
- Urine sample for gluten immunogenic peptides approximately 240 minutes after study drug administration. (Note: This sample should be obtained prior to the ingestion of food and liquids [normal diet] ad libitum.)
- Complete physical examination approximately 275 minutes after study drug administration
- ECG approximately 285 minutes after study drug administration
- NG tube removal approximately 80 minutes after study drug administration (i.e., after completion of the 65-minute post-dose gastric sampling and 70-minute post-dose vital signs)
- Ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration (i.e., after completion of the 125-minute post-dose AE recording and 130-minute post-dose GSQ), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides). (Note: The NG tube will have been removed prior to the ingestion of plain gluten-free food and liquids.)
- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review

- Remind subject of study restrictions as noted in Section 10
- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

7.2.11 Safety Visit (Part 2)

The Safety Visit will be conducted 5 ± 2 days after the subject's participation in the final Cohort Treatment Day, or 5 ± 2 days after participation in the last Cohort Treatment Day for a subject who withdraws early from the study and has received study drug (i.e., PvP001, PvP001 placebo, PvP002, or PvP002 comparator) on a previous Cohort Treatment Day(s).

If it is determined on Cohort Treatment Day -1 or pre-dose on the Cohort Treatment Day that a subject who has previously received study drug (i.e., PvP001, PvP001 placebo, PvP002, or PvP002 comparator) (i.e., on a prior Cohort Treatment Day[s]) is not eligible to proceed with the visit, the Cohort Treatment Day -1 and pre-dose Cohort Treatment Day procedures will serve as Safety Visit procedures.

If it is determined on Cohort Treatment Day -1 or pre-dose on the Cohort Treatment Day that a subject who has not previously received study drug (i.e., PvP001, PvP001 placebo, PvP002, or PvP002 comparator) (i.e., this is the subject's first Cohort Treatment Day) is not eligible to proceed with the visit, a Safety Visit will not be conducted.

A Safety Visit will be conducted 5 ± 2 days after the most recent dose of Nexium for a subject who withdraws early from the study, regardless of whether or not the subject has received study drug (i.e., PvP001 or PvP001 placebo).

The subject will be fasting (nothing by mouth except water) for at least 12 hours prior to the Safety Visit. The following procedures will be performed:

- AE recording
- Concomitant medication review
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Complete physical examination
- ECG
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Serum pregnancy test (in female)
- Urine drug screen
- Alcohol breathalyzer test

7.2.12 Follow Up Anti-Drug Antibody Blood Sampling Visits (Part 2)

Each subject will return to the Clinical Research Center for blood sampling for ADA testing 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day, unless the subject withdraws from the study before receiving any study drug (i.e., PvP001, PvP001 placebo, PvP002, or PvP002 comparator).

7.2.13 Cohort Treatment Days -1 (Part 3)

Admission to the Clinical Research Center on the day prior to the first Cohort Treatment Day will occur within 4 weeks of the Screening Visit.

The subject will report to the Clinical Research Center the afternoon prior to each of two Cohort Treatment Days, will eat a gluten-free dinner at the Clinical Research Center, and will subsequently begin an overnight fast (nothing by mouth for at least 12 hours).

At check in, the following procedures will be performed:

- Serum (first Cohort Treatment Day) or urine (second Cohort Treatment Day) pregnancy test (in female), urine drug screen, and alcohol breathalyzer test
  - Results must be reviewed on Cohort Treatment Day -1
    - If the pregnancy test or urine drug screen is positive, the subject will be withdrawn from the study
    - If the alcohol breathalyzer test is positive, the visit may be rescheduled at the discretion of, and if approved by, the Investigator and Medical Monitor
- Medical history (first Cohort Treatment Day) review or AE (second Cohort Treatment Day) recording
- Concomitant medication review
- Confirm ingestion of a GFD beginning the morning of Cohort Treatment Day -1

7.2.14 Cohort Treatment Days Pre-Dose (Part 3)

On the Cohort Treatment Day, the following procedures will be performed prior to NG tube placement:

- Confirm fasting status (nothing by mouth for at least 12 hours)
- Medical history (first Cohort Treatment Day) review or AE (second Cohort Treatment Day) recording
- GSQ
- Concomitant medication review
- Confirm ingestion of a GFD for 24 hours
- Vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight

- Complete physical examination
- ECG
- IV catheter placement
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Urine sample for gluten immunogenic peptides
- Inclusion and exclusion criteria review

On the Cohort Treatment Day, the following procedures will be performed prior to pretreatment buffer solution administration (Group 1), prior to study drug administration (Group 2, Group 4, and Group 5), or prior to ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3):

- NG tube placement with auscultation and gastric sampling (approximately 5 mL) for pH testing (to confirm NG tube placement and serve as the pretreatment pH measurement) and gluten quantification
- AE recording after NG tube placement
- GSQ after at least an approximately 15-minute waiting period following NG tube placement, or after a longer waiting period when any signs or symptoms that occur in association with the NG tube placement procedure, if applicable, have resolved or are considered non-severe and stable by the Investigator
- Vital signs after at least an approximately 15-minute waiting period following NG tube placement, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Blood sampling for PK immediately prior to pretreatment buffer solution administration (Group 1), prior to study drug administration (Group 2, Group 4, and Group 5), or prior to ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3) (pre-dose [time 0])

After completion of all the above study procedures in a Group 1 subject, the pretreatment buffer solution will be administered orally. Immediately after pretreatment buffer solution administration, study drug will be administered orally. Immediately after study drug administration, a standardized 1 g gluten-containing study meal will be ingested; ingestion of the entire study meal should be completed within 10 minutes of study drug administration.

After completion of all the above study procedures in a Group 2 or Group 5 subject, study drug will be administered orally. Immediately after study drug administration, a standardized 1 g gluten-containing study meal will be ingested; ingestion of the entire study meal should be completed within 10 minutes of study drug administration. (Note: No pretreatment buffer solution will be administered to a Part 3 Group 2 or Group 5 subject.)

After completion of all the above study procedures in a Group 3 subject, approximately 50 mL of a standardized 1 g gluten-containing study meal will be ingested; ingestion of the 50 mL portion of the study meal should be completed within 5 minutes. Immediately after ingestion of the 50 mL portion of the study meal, study drug will be administered orally. Immediately after study

drug administration, the remaining portion of the standardized 1 g gluten-containing study meal will be ingested; ingestion of this remaining portion of the study meal should be completed within 10 minutes of study drug administration. (Note: No pretreatment buffer solution will be administered to a Part 3 Group 3 subject.)

After completion of all the above study procedures in a Group 4 subject, study drug will be administered orally. Immediately after study drug administration, a standardized gluten-free study meal will be ingested; ingestion of the entire gluten-free study meal should be completed within 10 minutes of study drug administration. Thirty minutes after study drug administration, a standardized 1 g gluten-containing study meal will be ingested; ingestion of the entire gluten-containing study meal should be completed within 10 minutes. (Note: No pretreatment buffer solution will be administered to a Part 3 Group 4 subject.)

7.2.15 Cohort Treatment Days Post-Dose (Part 3)

7.2.15.1 Group 1, Group 2, and Group 5

After pretreatment buffer solution administration, study drug administration, and study meal ingestion have all been completed in a Group 1 subject, or after study drug administration and study meal ingestion have been completed in a Group 2 or Group 5 subject, the following procedures will be performed in a Group 1, Group 2 or Group 5 subject:

- Ask the subject to move approximately 10 minutes after study drug administration
- Aspiration of approximately 30-40 mL of gastric contents from the NG tube, followed by reinjection through the NG tube, using a 60 mL syringe approximately 10, 15, and 20 minutes after study drug administration
- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration
- AE recording approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report
- GSQ approximately 30, 130, and 325 minutes after study drug administration
- Gastric sampling for pH testing and gluten quantification
    - Gastric sampling (approximately 15 mL) 35 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 35 minutes after study drug administration.) The aspirated volume of the gastric sample will be measured before a portion is removed for pH testing and gluten quantification.
    - Gastric sampling (entire gastric content) 65 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 65 minutes after study drug administration.) The aspirated volume of the entire gastric content sample will be measured before a portion is removed for pH testing and gluten quantification.
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70, 190, and 270 minutes after study drug administration

- Clinical laboratory tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration (urinalysis may be done at a later time point [up to 480 minutes after study drug administration] if necessary)
- Urine sample for gluten immunogenic peptides approximately 240 minutes after study drug administration. (Note: This sample should be obtained prior to the ingestion of food and liquids [normal diet] ad libitum.)
- Complete physical examination approximately 275 minutes after study drug administration
- ECG approximately 285 minutes after study drug administration
- NG tube removal approximately 80 minutes after study drug administration (i.e., after completion of the 65-minute post-dose gastric sampling and 70-minute post-dose vital signs)
- Ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration (i.e., after completion of the 125-minute post-dose AE recording and 130-minute post-dose GSQ), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides). (Note: The NG tube will have been removed prior to the ingestion of plain gluten-free food and liquids.)
- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review
- Remind subject of study restrictions as noted in Section 10
- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

7.2.15.2 Group 3

After ingestion of the approximately 50 mL portion of the study meal, study drug administration, and ingestion of the remaining portion of the study meal have all been completed, the following procedures will be performed in a Group 3 subject:

- Ask the subject to move approximately 10 minutes after study drug administration
- Aspiration of approximately 30-40 mL of gastric contents from the NG tube, followed by reinjection through the NG tube, using a 60 mL syringe 10, 12, and 14 minutes after study drug administration
- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration

- AE recording approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report
- GSQ approximately 30, 130, and 325 minutes after study drug administration
- Gastric sampling for pH testing and gluten quantification
    - Gastric sampling (approximately 15 mL) 35 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 35 minutes after study drug administration.) The aspirated volume of the gastric sample will be measured before a portion is removed for pH testing and gluten quantification.
    - Gastric sampling (entire gastric content) 65 minutes after study drug administration. (Note: it is important to begin gastric sample aspiration 65 minutes after study drug administration.) The aspirated volume of the entire gastric content sample will be measured before a portion is removed for pH testing and gluten quantification.
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70, 190, and 270 minutes after study drug administration
- Clinical laboratory tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration (urinalysis may be done at a later time point [up to 480 minutes after study drug administration] if necessary)
- Urine sample for gluten immunogenic peptides approximately 240 minutes after study drug administration. (Note: This sample should be obtained prior to the ingestion of food and liquids [normal diet] ad libitum.)
- Complete physical examination approximately 275 minutes after study drug administration
- ECG approximately 285 minutes after study drug administration
- NG tube removal approximately 80 minutes after study drug administration (i.e., after completion of the 65-minute post-dose gastric sampling and 70-minute post-dose vital signs)
- Ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration (i.e., after completion of the 125-minute post-dose AE recording and 130-minute post-dose GSQ), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides). (Note: The NG tube will have been removed prior to the ingestion of plain gluten-free food and liquids.)
- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review
- Remind subject of study restrictions as noted in Section 10

- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

7.2.15.3 Group 4

After study drug administration and gluten-free study meal ingestion have been completed, the following procedures will be performed in a Group 4 subject:

- Ask the subject to move approximately 10 and 40 minutes after study drug administration
- Aspiration of approximately 30-40 mL of gastric contents from the NG tube, followed by reinjection through the NG tube, using a 60 mL syringe 10, 12, 14, 40, 45, and 50 minutes after study drug administration
- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration
- AE recording approximately 25, 125, 180, 320, and 460 minutes after study drug administration, and at any other time upon spontaneous subject report
- Ingestion of the 1 g gluten-containing study meal 30 minutes after study drug administration. (Note: It is important to begin ingestion 30 minutes after study drug administration.) Ingestion of the entire gluten-containing study meal should be completed within 10 minutes.
- Gastric sampling (entire gastric content) for pH testing and gluten quantification 65 minutes after study drug administration. (Note: It is important to begin gastric sample aspiration 65 minutes after study drug administration.) The aspirated volume of the entire gastric content sample will be measured before a portion is removed for pH testing and gluten quantification.
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70, 190, and 270 minutes after study drug administration
- GSQ approximately 130 and 325 minutes after study drug administration
- Clinical laboratory tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration (urinalysis may be done at a later time point [up to 480 minutes after study drug administration] if necessary)
- Urine sample for gluten immunogenic peptides approximately 240 minutes after study drug administration. (Note: This sample should be obtained prior to the ingestion of food and liquids [normal diet] ad libitum.)
- Complete physical examination approximately 275 minutes after study drug administration
- ECG approximately 285 minutes after study drug administration
- NG tube removal approximately 80 minutes after study drug administration (i.e., after completion of the 65-minute post-dose gastric sampling and 70-minute post-dose vital signs)
- Ingestion of plain gluten-free food (i.e., fresh uncooked fruits, fresh uncooked vegetables, hard-boiled eggs removed directly from their shells, unseasoned nuts removed directly

from their shells) and liquids (i.e., water, Gatorade, 100% fruit juice, 100% vegetable juice) may begin approximately 135 minutes after study drug administration (i.e., after completion of the 125-minute post-dose AE recording and 130-minute post-dose GSQ), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Ingestion of food and liquids (normal diet) ad libitum may begin approximately 255 minutes after study drug administration (i.e., after completion of the 240-minute post-dose urine sampling for gluten immunogenic peptides). (Note: The NG tube will have been removed prior to the ingestion of plain gluten-free food and liquids.)

- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review
- Remind subject of study restrictions as noted in Section 10
- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

7.2.16 Safety Visit (Part 3)

The Safety Visit will be conducted 5 ± 2 after the subject's participation in the final Cohort Treatment Day, or 5 ± 2 days after participation in the last Cohort Treatment Day for a subject who withdraws early from the study and has received study drug (i.e., PvP003 or PvP003 placebo) on a previous Cohort Treatment Day.

If it is determined on Cohort Treatment Day -1 or pre-dose on the Cohort Treatment Day that a subject who has previously received study drug (i.e., PvP003 or PvP003 placebo) (i.e., on a prior Cohort Treatment Day) is not eligible to proceed with the visit, the Cohort Treatment Day -1 and pre-dose Cohort Treatment Day procedures will serve as Safety Visit procedures.

If it is determined on Cohort Treatment Day -1 or pre-dose on the Cohort Treatment Day that a subject who has not previously received study drug (i.e., PvP003 or PvP003 placebo) (i.e., this is the subject's first Cohort Treatment Day) is not eligible to proceed with the visit, a Safety Visit will not be conducted.

The subject will be fasting (nothing by mouth except water) for at least 12 hours prior to the Safety Visit. The following procedures will be performed:

- AE recording
- Concomitant medication review
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Complete physical examination
- ECG
- Clinical laboratory tests (chemistry, hematology, and urinalysis)

- Serum pregnancy test (in female)
- Urine drug screen
- Alcohol breathalyzer test

7.2.17 Follow Up Anti-Drug Antibody Blood Sampling Visits (Part 3)

Each subject will return to the Clinical Research Center for blood sampling for ADA testing 14 ± 2 days and 28 ± 2 days after the final Cohort Treatment Day, unless the subject withdraws from the study before receiving any study drug (i.e., PvP003 or PvP003 placebo).

7.2.18 Cohort Treatment Period Days -1 and Days 4 (Part 4)

Admission to the Clinical Research Center on the day prior to Day 1 of the first Cohort Treatment Period will occur within 4 weeks of the Screening Visit.

The subject will report to the Clinical Research Center the afternoon prior to Day 1 of each Cohort Treatment Period (i.e., Day -1 of Cohort 4A Treatment Period and Day -1 of Cohort 4B Treatment Period) and the afternoon prior to Day 5 of each Cohort Treatment Period (i.e., Day 4 of Cohort 4A Treatment Period and Day 4 of Cohort 4B Treatment Period). On Day -1 of each Cohort Treatment Period, the subject will eat a regular meal (i.e., dinner) at the Clinical Research Center. On Day 4 of each Cohort Treatment Period, the third daily dose of study drug will be administered by study personnel immediately prior to the subject beginning the ingestion of a regular meal (i.e., dinner) at the Clinical Research Center. Each subject will subsequently begin an overnight fast (nothing by mouth except water for at least 12 hours).

At check in, the following procedures will be performed:

- Serum (Day -1 of the first Cohort Treatment Period) or urine (Day -1 of the second Cohort Treatment Period) pregnancy test (in female), and urine drug screen and alcohol breathalyzer test on Day -1 and Day 4 of each Cohort Treatment Period
    - Results must be reviewed on Day -1 and Day 4 of each Cohort Treatment Period
        - If the pregnancy test or urine drug screen is positive, the subject will be withdrawn from the study
        - If the alcohol breathalyzer test is positive on Day -1 of the first Cohort Treatment Period, the visit may be rescheduled at the discretion of, and if approved by, the Investigator and Medical Monitor; if the alcohol breathalyzer test is positive on Day -1 of the second Cohort Treatment Period or Day 4 of either Cohort Treatment Period, the subject will be withdrawn from the study
- Medical history (Day -1 of the first Cohort Treatment Period) review or AE (Day -1 of the second Cohort Treatment Period and Day 4 of each Cohort Treatment Period) recording
- Concomitant medication review
- On Day 4 of each Cohort Treatment Period, assess compliance with the study drug that was dispensed on Day 1 of the same Cohort Treatment Period using the subject's Daily PvP003 Dosing Diary and an inventory of the subject's returned study drug (PvP003

placebo or PvP003). (Note: The first and second daily doses of study drug on Day 4 of each Cohort Treatment Period will be self-administered immediately prior to beginning the ingestion of a regular meal [i.e., breakfast and lunch] before admission to the Clinical Research Center; the second daily dose on Day 4 will be the final dose of study drug that is self-administered during each Cohort Treatment Period. The subject will return study drug upon admission to the Clinical Research Center on Day 4 of each Cohort Treatment Period. The third daily dose of study drug on Day 4 of each Cohort Treatment Period will be administered by study personnel immediately prior to the subject beginning the ingestion of a regular meal [i.e., dinner].)

- On Day -1 of the second Cohort Treatment Period and Day 4 of each Cohort Treatment Period, review the GSQs (completed and not completed) that were dispensed on Day 1 of the first Cohort Treatment Period for the subject to complete, in order to ensure that the subject is completing them every day; collect the completed GSQs; remind the subject to complete the GSQ every day at bedtime through the day prior to the Safety Visit; and remind the subject to bring the GSQs (completed and not completed) to each visit at the Clinical Research Center through the Safety Visit.

7.2.19 Cohort Treatment Period Days 1 and Days 5 Pre-Dose (Part 4)

On Day 1 and Day 5 of each Cohort Treatment Period, the following procedures will be performed prior to administration of the first daily dose of study drug:

- Confirm fasting status (nothing by mouth except water for at least 12 hours)
- Medical history (Day 1 of the first Cohort Treatment Period) review or AE (Day 1 of the second Cohort Treatment Period and Day 5 of each Cohort Treatment Period) recording
- GSQ
- Concomitant medication review
- Ask the subject: “Did you generally follow a gluten-free or reduced gluten diet in the past 24 hours?” and record the answer as “yes” or “no”
- Vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Complete physical examination
- ECG
- IV catheter placement
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Urine sample for gluten immunogenic peptides
- Inclusion and exclusion criteria review
- Blood sampling for PK immediately prior to study drug administration (pre-dose [time 0])

After completion of all the above study procedures, study drug will be administered orally by study personnel. Immediately after study drug administration, the subject will begin to ingest a regular meal (i.e., breakfast).

7.2.20 Cohort Treatment Periods Days 1 and Days 5 Post-Dose (Part 4)

After administration of the first daily dose of study drug by study personnel on Day 1 of each Cohort Treatment Period, the following procedures will be performed:

- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, and 240 minutes after study drug administration
- AE recording approximately 40, 125, and 180 minutes after study drug administration, and at any other time upon spontaneous subject report
- GSQ approximately 50 and 130 minutes after study drug administration
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, approximately 70 and 190 minutes after study drug administration
- Complete physical examination approximately 215 minutes after study drug administration
- ECG approximately 225 minutes after study drug administration
- Clinical laboratory tests (chemistry, hematology, and urinalysis) approximately 240 minutes after study drug administration
- Ingestion of any type of snack food and liquids may begin approximately 135 minutes after administration of the first daily dose of study drug (i.e., after completion of the 125-minute post-dose AE recording and 130-minute post-dose GSQ), provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Approximately 255 minutes after administration of the first daily dose of study drug (i.e., after completion of the 240-minute post-dose PK sampling and clinical laboratory tests), the second daily dose of study drug will be administered orally by study personnel and the subject will immediately begin to ingest a regular meal (i.e., lunch).
- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review
- Remind subject of study restrictions as noted in Section 10
- On Day 1 of each Cohort Treatment Period, dispense study drug (PvP003 placebo or PvP003) for self-administration and train the subject on dosing and completion of the Daily PvP003 Dosing Diary. (Note: The first self-administered dose of study drug [PvP003 placebo or PvP003] on Day 1 of each Cohort Treatment Period will be the third daily dose, which the subject will take immediately prior to beginning the ingestion of a regular meal [i.e., dinner].)
- On Day 1 of the first Cohort Treatment Period, dispense all GSQs for the subject to complete through the Safety Visit. Instruct the subject to complete the GSQ every day at bedtime starting on Day 1 of the first Cohort Treatment Period and continuing through

the day prior to the Safety Visit, and to bring the GSQs (completed and not completed) to each visit at the Clinical Research Center through the Safety Visit.

- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

After administration of the first daily dose of study drug by study personnel on Day 5 of each Cohort Treatment Period, the following procedures will be performed:

- Blood sampling for PK approximately 15, 30, 45, 60, 120, 180, and 240 minutes after study drug administration
- Ingestion of any type of snack food and liquids may begin approximately 135 minutes after administration of the first daily dose of study drug, provided, if applicable, any gastrointestinal symptoms or signs have resolved or are considered stable by the Investigator. Approximately 255 minutes after administration of the first daily dose of study drug (i.e., after completion of the 240-minute post-dose PK sampling), the second daily dose of study drug will be administered orally by study personnel and the subject will immediately begin to ingest a regular meal (i.e., lunch).
- The IV catheter may be removed after the final post-dose blood samples are drawn
- Concomitant medication review
- AE recording
- Remind subject of study restrictions as noted in Section 10
- After completion of all study procedures, the subject will be discharged from the Clinical Research Center when the Investigator determines that the subject is in stable condition

7.2.21 Safety Visit (Part 4)

The Safety Visit will be conducted 5 ± 2 days after the subject's final dose of study drug (i.e., 5 ± 2 days after Day 5 of the second Cohort Treatment Period), or after the subject's last dose of study drug for a subject who withdraws early from the study and has received study drug (i.e., PvP003 or PvP003 placebo).

If it is determined on Day -1 of the first Cohort Treatment Period or pre-dose on Day 1 of the first Cohort Treatment Period that a subject who has not previously received study drug (i.e., PvP003 or PvP003 placebo) is not eligible to proceed with the visit, a Safety Visit will not be conducted.

If it is determined on Day -1 of the second Cohort Treatment Period or pre-dose on Day 1 of the second Cohort Treatment Period that a subject who has previously received study drug (i.e., PvP003 or PvP003 placebo) is not eligible to proceed with the visit, the procedures on Day -1 of the second Cohort Treatment Period and pre-dose on Day 1 of the second Cohort Treatment Period will serve as Safety Visit procedures.

If it is determined on Day 4 of the first or second Cohort Treatment Period or pre-dose on Day 5 of the first or second Cohort Treatment Period that a subject who has previously received study

drug (i.e., PvP003 or PvP003 placebo) is not eligible to proceed with the visit, the procedures on Day 4 of the first or second Cohort Treatment Period and pre-dose on Day 5 of the first or second Cohort Treatment Period will serve as Safety Visit procedures.

The subject will be fasting (nothing by mouth except water) for at least 12 hours prior to the Safety Visit. The following procedures will be performed:

- AE recording
- Concomitant medication review
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature
- Weight
- Complete physical examination
- ECG
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Serum pregnancy test (in female)
- Urine drug screen
- Alcohol breathalyzer test
- Collect all remaining GSQs (completed and not completed)

7.2.22 Follow Up Anti-Drug Antibody Blood Sampling Visits (Part 4)

Each subject will return to the Clinical Research Center for blood sampling for ADA testing 14 ± 2 days and 28 ± 2 days after Day 5 of the second Cohort Treatment Period, unless the subject withdraws from the study before receiving any study drug (i.e., PvP003 or PvP003 placebo).

7.2.23 Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the subject's request, or as deemed necessary by the Investigator. The date and reason for the unscheduled visit, as well as the procedures performed, will be documented. The performance of special testing (i.e., other than the per protocol testing performed during the study) that the Investigator deems necessary or other recommendations should be discussed in advance with the Medical Monitor or designee, if the subject's clinical status allows.

7.3 Premature Discontinuation

Withdrawal of a subject from the study may occur at any time. However, in this case, a subject who has received study drug (i.e., PvP001, PvP001 placebo, PvP002, PvP002 comparator, PvP003, or PvP003 placebo) will be encouraged to complete the Safety Follow Up Call (Part 1) or Safety Visit (Part 2, Part 3, and Part 4) and the 14 ± 2 days and 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visits before withdrawing from the study, and a subject who has received Nexium, regardless of whether or not the subject has received study drug (i.e., PvP001 or PvP001 placebo), will be encouraged to complete the Safety Visit (Part 2). The reason for withdrawal will be documented. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Significant subject noncompliance, defined as inability or unwillingness to complete the procedures defined in the Schedule of Assessments (see Section 4.4), and missed or late study visits;
- Subject is lost to follow up (i.e., staff unable to contact the subject after several attempts);
- Request of the subject or Investigator;
- Clinically significant abnormal laboratory or other test result; or
- Development of any AE, condition, intercurrent illness, injury, or medical condition, or use of a restricted medication that is likely to interfere with the subject's safety, the overall assessment, or the study procedures.

In addition, the Sponsor reserves the right to discontinue this clinical study at any time for any reason. Such a termination must be implemented by the Investigator in a time frame that is compatible with subject well-being.

7.3.1 Replacement Subjects

Part 1

Subjects who withdraw early from the study for reasons other than AEs will be replaced.

Part 2, Part 3, and Part 4

Subjects who withdraw early from the study may be replaced, based on Sponsor decision.

8 STUDY DRUG

8.1 Study Drug Description

PvP001 is a liquid containing the active enzyme, Kuma062, in a formulation buffer CCI [redacted] It will be supplied as a frozen liquid in single-use 5 mL screw-cap polypropylene cryogenic vials, each of which contains approximately 3.5 mL of PvP001 at a concentration of 100 mg/mL.

PvP001 will be thawed approximately 15 minutes prior to the time of planned administration by gently rolling the vial between the hands until thawed and then gently inverting (not shaking) the vial approximately eight times, being careful to prevent foaming to preserve protein stability. Immediately prior to administration, to achieve the required PvP001 dose to be administered, sterile water will be poured into a polypropylene cup to the approximately 70-80 mL line. Study personnel will then slowly (to avoid air bubbles to preserve protein stability) pipette a specified volume of thawed PvP001 from the vial and add this to the sterile water. The contents of the cup will be gently swirled a few times to mix. Additional sterile water, to a total volume of 100 mL, will be added to the cup and the contents of the cup will again be gently swirled a few times to mix. The total volume of PvP001 plus sterile water will be the same (100 mL) for all PvP001 doses. The volumes of thawed PvP001 and sterile water to achieve each required PvP001 dose in a total volume of 100 mL are shown in Table 9.

Table 9. Dilution of PvP001

Desired PvP001 Dose (mg)	PvP001 Concentration in Each Vial Before Dilution (mg/mL)	PvP001 Volume Taken from Vial(s) (mL)	Total Sterile Water Volume Added (mL)	Final PvP001 + Sterile Water Volume (mL)	Final PvP001 Concentration in 100 mL (mg/mL)
Placebo	100	-	100	100	0
100		1	99		1
300		3	97		3
600		6	94		6
900		9	91		9

CCI [redacted] The MFD of PvP002 will be administered and will be based on the amount of enzyme included in each capsule and the maximum number of capsules that can easily be swallowed by a subject with 100 mL of sterile water. The MFD of PvP002 is expected to be in the range of 300-400 mg (e.g., 3-4 capsules, each containing 100 mg of active enzyme), but will not exceed the MTD of PvP001.

PvP003 300 mg is a tablet containing the same active enzyme, Kuma062, CCI [redacted] The tablet is tasteless, capsule-shaped, unmarked, and white to off-white.

The pretreatment buffer solution will be prepared according to Appendix A.

Sterile water for dilution of PvP001, for PvP001 placebo, for PvP002 comparator, for preparation of the pretreatment buffer solution, and for swallowing PvP002 and PvP003 will be United States Pharmacopeia (USP) for injection with 0 osmolarity.

One gram of PEG 3350 (MiraLAX®; polyethylene glycol 3350 unflavored grit-free powder for solution) will be added to and blended with the other ingredients at the time the standardized gluten-containing study meal is prepared and will serve as a marker of total gastric volume. It is taste-, preservative-, sugar-, and gluten-free.

8.1.1 Placebo/Comparator Description

The PvP001 placebo will be sterile water. The volume of PvP001 placebo will be 100 mL. Diluted PvP001 is essentially tasteless and colorless, and the sterile water is tasteless and colorless. Therefore, no taste or color masking will be done. PvP001 placebo will be administered in a cup that is identical to the cup used to administer PvP001 active treatment.

The PvP002 comparator will be sterile water. The volume of PvP002 comparator will be 100 mL. There is no capsule placebo for PvP002.

The PvP003 placebo will be a tablet CCI [redacted], indistinguishable by taste and appearance (e.g., shape, size, color) from the PvP003 300 mg tablet.

8.2 Packaging, Labeling, Shipment, and Storage

PvP001 will be shipped to the clinical site as a frozen (-80 °C ± 10 °C) liquid in single-use 5 mL screw-cap polypropylene cryogenic vials. Each vial will contain approximately 3.5 mL of PvP001 at a concentration of 100 mg/mL. PvP001 will be stored at the clinical site at a temperature of -80 °C ± 10 °C. Each vial will be labeled with the protocol number, storage conditions, federal cautionary statement, and Sponsor name and address. The Investigator or designee will annotate the label to include the subject number.

PvP002 will be shipped to the clinical site as refrigerated (2-8 °C) capsules in single-use bottles. Each bottle will contain four 100 mg PvP002 capsules. Each bottle will be contained in a foil pouch to protect against moisture and will be stored refrigerated (2-8 °C) at the clinical site. Each bottle and pouch will be labeled with the protocol number, storage conditions, federal cautionary statement, and Sponsor name and address. The Investigator or designee will annotate the label to include the subject number.

PvP003 300 mg will be shipped to the clinical site as refrigerated (2-8 °C) tablets in foil blisters on cards, with three cards in each carton. Each card will have eight foil blisters. Each foil blister will contain one PvP003 300 mg tablet. Each card will be stored refrigerated (2-8 °C) at the clinical site, as well as outside of the clinical site for a Part 4 subject. Each carton and card will be labeled with the protocol number, storage conditions, federal cautionary statement, and Sponsor name and address. PvP003 300 mg tablets may be dispensed to more than one Part 3 subject from the same card.

PvP003 placebo will be shipped to the clinical site as refrigerated (2-8 °C) tablets in foil blisters on cards, with three cards in each carton. Each card will have eight foil blisters. Each foil blister will contain one PvP003 placebo tablet. Each card will be stored refrigerated (2-8 °C) at the clinical site, as well as outside of the clinical site for a Part 4 subject. Each carton and card will be labeled with the protocol number, storage conditions, federal cautionary statement, and Sponsor name and address. PvP003 placebo tablets may be dispensed to more than one Part 3 subject from the same card.

Sterile water will be supplied by the Sponsor to the clinical site at room temperature in screw-top 500 mL bottles. Sterile water will be stored at the clinical site at room temperature, in accordance with the manufacturer's instructions. Each bottle will be labeled with the manufacturer's label. All sterile water used in this study will be supplied by the Sponsor.

The pretreatment buffer solution will be shipped to the clinical site as a refrigerated (2-8 °C) liquid in single-use amber bottles. Each bottle will contain 50 mL of pretreatment buffer solution. Pretreatment buffer solution will be stored at the clinical site refrigerated (2-8 °C). Each bottle will be labeled with the contents, protocol number, storage conditions, Sponsor name and address, and compounding pharmacy name and address. The Investigator or designee will annotate the label to include the subject number and date dispensed.

Nexium (Nexium® 24HR) will be supplied by the Sponsor to the clinical site. Each bottle will contain 14 capsules of Nexium 20 mg, as packaged by the manufacturer. Nexium will be stored at the clinical site at room temperature, in accordance with the manufacturer's instructions. Each bottle will be labeled with the manufacturer's label. Each sealed bottle will be designated for a single subject. Upon dispensing to the subject, the clinical site pharmacy will apply a label complying with its pharmacy standards that includes the protocol number, subject number, and date dispensed to the subject.

Polyethylene glycol 3350 (MiraLAX®; polyethylene glycol 3350 unflavored grit-free powder for solution) will be supplied by the Sponsor to the clinical site as a room temperature powder in a 765-gram container. The powder will be stored at the clinical site at room temperature, in accordance with the manufacturer's instructions. Each container will be labeled with the manufacturer's label.

Upon receipt of the study drug supplies, it is the responsibility of the Investigator or designee to ensure that records of inventory and accountability are maintained. Study drug supplies and records must be readily available for inspection by the Sponsor or its representatives and regulatory authorities at any time.

8.3 Dose and Administration

Part 1

Immediately prior to administration of study drug, each subject will drink 50 mL of pretreatment buffer solution from a cup and swallow, as rapidly as possible.

Immediately after administration of the pretreatment buffer solution (i.e., within 5 minutes), each subject will drink 100 mL of study drug (PvP001) from a cup or will swallow all capsules of study drug (PvP002) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow all PvP002 capsules, the lowest additional volume needed will be used.

A single dose of PvP001 placebo, PvP001 100 mg, PvP001 300 mg, PvP001 900 mg, or PvP002 will be administered on the Cohort 1A, 1B, 1C, 1D, or 1E Treatment Day, respectively.

Immediately after administration of study drug, each subject will ingest the standardized gluten-free study meal; the entire study meal will be ingested within 10 minutes of study drug administration.

Part 2

Immediately prior to administration of study drug, each subject will drink 50 mL of pretreatment buffer solution from a cup and swallow, as rapidly as possible.

Immediately after administration of the pretreatment buffer solution (i.e., within 5 minutes), each subject will drink 100 mL of study drug (PvP001) from a cup or will swallow all capsules of study drug (PvP002) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow all PvP002 capsules, the lowest additional volume needed will be used.

A Group 1 subject will be treated with a single dose of PvP001 placebo, the MTD of PvP001 from Part 1 of the study, and the MTD of PvP001 from Part 1 of the study following 7 days of treatment with a standard dose of a PPI on the Cohort 2A, 2B, and 2C Treatment Days, respectively.

A Group 2 subject will be treated with a single dose of the PvP002 comparator (sterile water) and the MFD of PvP002 on the Cohort 2D and 2E Treatment Days, respectively.

A Group 3 subject will be treated with a single dose of PvP001 placebo on the Cohort 2F or 2I Treatment Day and a single dose of PvP001 300 mg, 600 mg, or 900 mg on the Cohort 2G, 2H, or 2J Treatment Day, respectively.

Immediately after administration of study drug, each subject will ingest the standardized gluten-containing study meal; the entire study meal will be ingested within 10 minutes of study drug administration.

Part 3

Group 1

Immediately prior to administration of study drug, each Group 1 subject will drink 50 mL of pretreatment buffer solution from a cup and swallow, as rapidly as possible.

Immediately after administration of the pretreatment buffer solution (i.e., within 5 minutes), each subject will swallow two tablets of study drug (PvP003 placebo or PvP003 300 mg) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow both PvP003 tablets, the lowest additional volume needed will be used.

A Group 1 subject will be treated with a single dose of PvP003 placebo on the Cohort 3A Treatment Day and a single dose of PvP003 600 mg on the Cohort 3B Treatment Day.

Immediately after administration of study drug, each subject will ingest the standardized 1 g gluten-containing study meal; the entire study meal will be ingested within 10 minutes of study drug administration.

Group 2

Each subject will swallow two tablets of study drug (PvP003 placebo or PvP003 300 mg) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow both PvP003 tablets, the lowest additional volume needed will be used.

A Group 2 subject will be treated with a single dose of PvP003 placebo on the Cohort 3C Treatment Day and a single dose of PvP003 600 mg on the Cohort 3D Treatment Day.

Immediately after administration of study drug, each subject will ingest the standardized 1 g gluten-containing study meal; the entire study meal will be ingested within 10 minutes of study drug administration.

Group 3

Each subject will ingest approximately 50 mL of the standardized 1 g gluten-containing study meal; the approximately 50 mL portion of the study meal will be ingested within 5 minutes. Immediately after ingestion of the approximately 50 mL portion of the study meal, each subject will swallow two tablets of study drug (PvP003 placebo or PvP003 300 mg) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow both PvP003 tablets, the lowest additional volume needed will be used.

A Group 3 subject will be treated with a single dose of PvP003 placebo on the Cohort 3E Treatment Day and a single dose of PvP003 600 mg on the Cohort 3F Treatment Day.

Immediately after administration of study drug, each subject will ingest the remaining portion of the standardized 1 g gluten-containing study meal; this remaining portion of the study meal will be ingested within 10 minutes of study drug administration.

Group 4

Each subject will swallow two tablets of study drug (PvP003 placebo or PvP003 300 mg) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow both PvP003 tablets, the lowest additional volume needed will be used.

A Group 4 subject will be treated with a single dose of PvP003 placebo on the Cohort 3G Treatment Day and a single dose of PvP003 600 mg on the Cohort 3H Treatment Day.

Immediately after administration of study drug, each subject will ingest the standardized gluten-free study meal; the entire gluten-free study meal will be ingested within 10 minutes of study drug administration. Thirty minutes after administration of study drug, each subject will ingest the standardized 1 g gluten-containing study meal; the entire gluten-containing study meal will be ingested within 10 minutes.

Group 5

Prior to dosing, one PvP003 placebo tablet or PvP003 300 mg tablet will be cut approximately in half during the subject's admission at the Clinical Research Center. The dose will be confirmed by the weight of the split tablet and must be within 10% of the target weight for half of a tablet.

Each subject will swallow approximately one half of a tablet of study drug (PvP003 placebo or PvP003 300 mg) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow the PvP003 tablet, the lowest additional volume needed will be used.

A Group 5 subject will be treated with a single dose of PvP003 placebo on the Cohort 3I Treatment Day and a single dose of PvP003 150 mg on the Cohort 3J Treatment Day.

Immediately after administration of study drug, each subject will ingest the standardized 1 g gluten-containing study meal; the entire study meal will be ingested within 10 minutes of study drug administration.

Part 4

During the subject's admission at the Clinical Research Center, study drug will be administered by study personnel. Each subject will swallow two tablets of study drug (PvP003 placebo or PvP003 300 mg) with 100 mL of sterile water, as rapidly as possible. If more than 100 mL of sterile water is needed to swallow both PvP003 tablets, the lowest additional volume needed will be used.

Study drug will be self-administered outside of the Clinical Research Center (e.g., at home, at work). Each subject will swallow two tablets of study drug (PvP003 placebo or PvP003 300 mg) with water (e.g., tap or bottled) in the amount needed, as rapidly as possible.

A Part 4 subject will be treated with a dose of PvP003 placebo TID during the 5-day Cohort 4A Treatment Period and a dose of PvP003 600 mg TID during the 5-day Cohort 4B Treatment Period.

Immediately after administration of each dose of study drug TID, each subject will begin to ingest a regular meal (i.e., breakfast, lunch, and dinner); there will be no limit on the amount of time after study drug administration that the subject has to ingest the regular meal, but the regular meal should be ingested in "one sitting."

8.4 Accountability and Compliance

Part 1 and Part 2

Study personnel will observe the subject during pretreatment buffer solution administration to ensure that the entire 50 mL volume is swallowed.

Study personnel will observe the subject during PvP001 administration to ensure that the entire 100 mL volume is swallowed within 5 minutes of swallowing the pretreatment buffer solution.

Study personnel will observe the subject during PvP002 administration to ensure that all capsules are swallowed with 100 mL of sterile water within 5 minutes of swallowing the pretreatment buffer solution. In the event that more than 100 mL of sterile water is needed to swallow all PvP002 capsules, the additional volume will be documented. Research staff will confirm that no capsules are retained in the subject's hand or mouth.

Study personnel will observe the subject during PvP002 comparator (sterile water) administration to ensure that the entire 100 mL volume is swallowed within 5 minutes of swallowing the pretreatment buffer solution.

Study personnel will observe the subject during ingestion of the study meal to ensure that the entire meal is ingested within 10 minutes of swallowing the study drug.

Part 2

Each Group 1 subject will take Nexium 20 mg capsules once daily at bedtime beginning 7 days prior to the subject's scheduled Cohort 2C Treatment Day. It will be taken by the subject at approximately the same time each day. Nexium capsules will be provided to the subject for home administration of 6 consecutive daily doses. The final dose (dose 7) of Nexium will be administered to the subject by the Clinical Research Center personnel at bedtime the night before the Cohort 2C Treatment Day (i.e., on Cohort 2C Treatment Day -1).

Each subject will be asked to complete a Daily Nexium Dosing Diary (see Appendix B) to document the date and time of day each Nexium dose is taken. Compliance with the Nexium pretreatment regimen will be assessed at check in on Cohort 2C Treatment Day -1. Compliance will be assessed using the subject's Daily Nexium Dosing Diary and an inventory of the subject's returned Nexium capsules. Compliance with Nexium will be considered acceptable if the subject has dosed 4 to 7 days and no doses were missed during the 4-day period before Cohort 2C Treatment Day -1. If a subject has taken Nexium consecutively for <4 days before Cohort 2C Treatment Day -1, the Cohort 2C Treatment Day visit can be rescheduled to allow the subject to take at least a 4-day course at home, provided the subject is otherwise eligible to

continue study participation. The subject will be questioned regarding any discrepancies from expected dosing.

Upon completion of Nexium dosing at home, unused Nexium will be returned by the subject to the clinical site.

Part 3

Group 1

Study personnel will observe the subject during pretreatment buffer solution administration to ensure that the entire 50 mL volume is swallowed.

Study personnel will observe the subject during PvP003 administration to ensure that both tablets are swallowed with 100 mL of sterile water within 5 minutes of swallowing the pretreatment buffer solution.

Study personnel will observe the subject during ingestion of the study meal to ensure that the entire meal is ingested within 10 minutes of swallowing the study drug.

Group 2

Study personnel will observe the subject during PvP003 administration to ensure that both tablets are swallowed with 100 mL of sterile water.

Study personnel will observe the subject during ingestion of the study meal to ensure that the entire meal is ingested within 10 minutes of swallowing the study drug.

Group 3

Study personnel will observe the subject during ingestion of the approximately 50 mL portion of the study meal to ensure that this portion of the meal is ingested within 5 minutes.

Study personnel will observe the subject during PvP003 administration to ensure that both tablets are swallowed with 100 mL of sterile water.

Study personnel will observe the subject during ingestion of the remaining portion of the study meal to ensure that this portion of the meal is ingested within 10 minutes of swallowing the study drug.

Group 4

Study personnel will observe the subject during PvP003 administration to ensure that both tablets are swallowed with 100 mL of sterile water.

Study personnel will observe the subject during ingestion of the gluten-free study meal to ensure that the entire meal is ingested within 10 minutes of swallowing the study drug.

Study personnel will observe the subject during ingestion of the gluten-containing study meal to ensure that the entire meal is ingested within 10 minutes.

Group 5

Study personnel will observe the subject during PvP003 administration to ensure that the approximately half of a tablet is swallowed with 100 mL of sterile water.

Study personnel will observe the subject during ingestion of the study meal to ensure that the entire meal is ingested within 10 minutes of swallowing the study drug.

Group 1, Group 2, Group 3, Group 4, and Group 5

In the event that more than 100 mL of sterile water is needed to swallow the PvP003 tablets, the additional volume will be documented. Research staff will confirm that no tablets are retained in the subject's hand or mouth.

Part 4

During the subject's admission at the Clinical Research Center, study personnel will observe the subject during PvP003 administration to ensure that both tablets are swallowed with 100 mL of sterile water. In the event that more than 100 mL of sterile water is needed to swallow both PvP003 tablets, the additional volume will be documented. Research staff will confirm that no tablets are retained in the subject's hand or mouth.

During the subject's admission at the Clinical Research Center, study personnel will observe the subject after PvP003 administration to ensure that the subject begins to ingest the regular meal immediately after (within 5 minutes) swallowing the study drug.

Each subject will self-administer two PvP003 tablets TID for 5 days during each Cohort Treatment Period (i.e., two PvP003 placebo tablets TID during the Cohort 4A Treatment Period and two PvP003 300 mg tablets TID during the Cohort 4B Treatment Period) immediately prior to (within 5 minutes) beginning the ingestion of a regular meal TID (i.e., breakfast, lunch, and dinner). If a meal is skipped, the PvP003 dose that would have been taken before the meal will be skipped. If a subject forgets to take a dose of PvP003 before a meal and has finished eating the meal, the PvP003 dose that would have been taken before the meal will be skipped. If a subject forgets to take a dose of PvP003 before a meal but has not finished eating the meal, the PvP003 dose will be taken before finishing the meal.

Study drug will be packaged in cartons, with three cards per carton and eight tablets per card. Either 5-day Cohort Treatment Period, or both, may be extended by 1 day if necessary. To complete the Cohort 4A Treatment Period, each subject will require up to 36 PvP003 placebo tablets; six cards (two cartons) with eight foil blisters on each card (i.e., a total of 48 PvP003 placebo tablets) will be dispensed on Day 1 of the Cohort 4A Treatment Period. To complete the Cohort 4B Treatment Period, each subject will require up to 36 PvP003 300 mg tablets; six cards (two cartons) with eight foil blisters on each card (i.e., a total of 48 PvP003 300 mg tablets) will be dispensed on Day 1 of the Cohort 4B Treatment Period. On Day 1 of each Cohort Treatment

Period, study personnel will administer two tablets (i.e., PvP003 placebo or PvP003 according to the subject's treatment assignment) before the subject eats breakfast and two tablets before the subject eats lunch; the subject will be discharged from the Clinical Research Center with the remaining 44 tablets for the current Cohort Treatment Period. After discharge from the Clinical Research Center on Day 1 of each Cohort Treatment Period, the subject will self-administer two tablets before eating dinner. On Day 2 and Day 3 of each Cohort Treatment Period, the subject will self-administer two tablets before eating breakfast, before eating lunch, and before eating dinner. On Day 4 of each Cohort Treatment Period, the subject will self-administer two tablets before eating breakfast and before eating lunch; at check in at the Clinical Research Center in the afternoon, the subject will return all six cards (those with and without remaining tablets) in their cartons and compliance will be assessed. On Day 4 of each Cohort Treatment Period, study personnel will administer two tablets before the subject eats dinner. On Day 5 of each Cohort Treatment Period, study personnel will administer two tablets before the subject eats breakfast and before the subject eats lunch; the dose before lunch on Day 5 of each Cohort Treatment Period will be the final dose of study drug for the current Cohort Treatment Period. (Note: If a Cohort Treatment Period is extended by one day, the subject will self-administer two tablets before eating dinner on Day 1 and two tablets before eating breakfast, before eating lunch, and before eating dinner on Day 2, Day 3, and Day 4. The subject will self-administer two tablets before eating breakfast and before eating lunch on Day 5; at check in at the Clinical Research Center in the afternoon, the subject will return all six cards in their cartons and compliance will be assessed. On Day 5, study personnel will administer two tablets before the subject eats dinner. On Day 6, study personnel will administer two tablets before the subject eats breakfast and before the subject eats lunch; the dose before lunch on Day 6 will be the final dose of study drug for the current Cohort Treatment Period.)

Each subject will be asked to complete a Daily PvP003 Dosing Diary (see Appendix C) to document the date and time of day each self-administered dose of study drug is taken. Compliance with study drug will be assessed at check in on Day 4 of each Cohort Treatment Period (or at check in on Day 5 of a Cohort Treatment Period that is extended by one day). Compliance will be assessed using the subject's Daily PvP003 Dosing Diary and an inventory of the subject's returned study drug tablets. Compliance with study drug during the current Cohort Treatment Period will be considered acceptable if the subject receives at least two (approximately 67%) of the three expected daily doses each day on Day 1, Day 2, Day 3, and Day 4 (and Day 5, if applicable), including the third daily dose that site personnel will administer before dinner on Day 4 (or Day 5, if applicable). The subject will be questioned regarding any discrepancies from expected dosing. The subject will be withdrawn from the study if the subject's compliance during the current Cohort Treatment Period is less than 67%.

9 DESCRIPTION OF STUDY PROCEDURES

Specific study procedures are described below. The study visits and time points during study visits at which these procedures are performed are included in Section 4.4 (see Table 5, Table 6, Table 7, and Table 8) and in Section 7.2.

Safety of PvP001, PvP002, and PvP003 will be assessed by collection and review of AEs, GSQs, physical examinations, vital signs, weight assessments, clinical laboratory tests (chemistry, hematology, and urinalysis), ADA testing, serum and urine pregnancy tests (in females), and ECGs. The GSQ is being used as a separate safety monitoring tool in this study to ensure that all gastrointestinal complaints are reported by the subject. The PK profile of PvP001 and PvP002 will be assessed using blood samples obtained in Part 1 and Part 2 of the study. The PK profile of PvP003 will be assessed using blood samples obtained in Part 3 and Part 4 of the study. The efficacy of PvP001, PvP002, and PvP003 will be assessed by evaluating gluten degradation in gastric samples obtained via an NG tube in Part 2 and Part 3 of the study.

9.1 Standardized Study Meal

A standardized blended study meal will be administered to subjects in this study. This meal is intended to be similar to the meal in the study reported by Siegel 2012, as discussed in the IB.

Four versions of this standardized blended study meal will be administered in this study. One meal is gluten-free (it includes bread that is gluten-free) and will be administered in Part 1 of the study to both healthy subjects and patients with CeD and in Part 3 of the study to healthy subjects in Group 4 (Cohorts 3G and 3H) (see Appendix D). Another meal contains 3 g of gluten (it includes bread with 3 g of gluten) and PEG 3350 and will be administered in Part 2 of the study to healthy subjects in Group 1 (Cohorts 2A, 2B, and 2C) and Group 2 (Cohorts 2D and 2E) (see Appendix E). Another meal contains 1 g of gluten (it includes bread with 1 g of gluten) and PEG 3350 and will be administered in Part 2 of the study to healthy subjects in Group 3 (Cohorts 2F, 2G, and 2H) and in Part 3 of the study to healthy subjects in Group 1 (Cohorts 3A and 3B), Group 2 (Cohorts 3C and 3D), Group 3 (Cohorts 3E and 3F), Group 4 (Cohorts 3G and 3H), and Group 5 (Cohorts 3I and 3J) (see Appendix F). Another meal contains 6 g of gluten (it includes bread with 3 g of gluten as well as 3 g of gluten powder added to the meal) and PEG 3350 and will be administered in Part 2 of the study to healthy subjects in Group 3 (Cohorts 2I and 2J) (see Appendix G). Except for the bread and gluten powder, all other ingredients of the study meals are the same. The approximate volume of all study meals is 300 mL. A complete list of the ingredients, weight and energy content of each ingredient, weight and energy content of all ingredients combined, and instructions for preparation, handling, and storage of the gluten-free meal, the 3 g gluten-containing meal, the 1 g gluten-containing meal, and the 6 g gluten-containing meal are included in Appendix D, Appendix E, Appendix F, and Appendix G, respectively.

One gram of PEG 3350 powder, taken from a multidose container and weighed, will be added to and blended with the other ingredients at the time the standardized gluten-containing study meal is prepared and will serve as a marker of dilution by endogenous gastric secretions. It is taste-, preservative-, sugar-, and gluten-free, and contains no inactive ingredients. The weight and

relative energy content of the study meal will not be altered significantly by the addition of this very low amount of PEG powder.

Ingestion of the study meal will begin immediately after completion of study drug administration. The entire study meal will be ingested by the subject within 10 minutes of completion of study drug administration.

Part 1

The objective of Part 1 of this study is to evaluate the safety of PvP001 and PvP002 administered to healthy subjects and to patients with CeD, rather than to evaluate the gluten-degrading activity of PvP001 and PvP002. Thus, patients with CeD who are on a GFD will be enrolled in this part of the study, will maintain a GFD during study participation, and will not be challenged with a gluten-containing meal. As it is important to administer the same meal to both healthy subjects and patients with CeD, a standardized gluten-free study meal will be administered to both healthy subjects and patients with CeD in this part of the study.

Part 2

The standardized 3 g gluten-containing study meal will be administered to Group 1 and Group 2 subjects in Part 2 of this study to evaluate the ability of PvP001 and PvP002 to degrade 3 g of gluten in healthy adult subjects. The amount of gluten (3 g) in this study meal was selected based on the gluten degradation capabilities observed under simulated gastric conditions in the laboratory, as discussed in the IB.

The standardized 1 g and 6 g gluten-containing study meals will be administered to Group 3 subjects in Part 2 of this study to evaluate the ability of PvP001 to degrade 1 g of gluten and 6 g of gluten in healthy adult subjects. The amounts of gluten (1 g and 6 g) in these study meals were selected based on the amount of gluten in the meal in the study reported by Siegel 2012 and on the gluten degradation capabilities observed under simulated gastric conditions in the laboratory, as discussed in the IB.

Part 3

The standardized 1 g gluten-containing study meal will be administered to Group 1, Group 2, Group 3, Group 4, and Group 5 subjects in Part 3 of this study to evaluate the ability of PvP003 to degrade 1 g of gluten in healthy adult subjects. (Note: The standardized 1 g gluten-containing study meal administered to Part 3 subjects will be identical to the standardized 1 g gluten-containing meal administered to Part 2 Group 3 subjects.) The amount of gluten (1 g) in this study meal was selected based on the amount of gluten in the meal in the study reported by Siegel 2012 and on the gluten degradation capabilities observed under simulated gastric conditions in the laboratory, as discussed in the IB.

The standardized gluten-free study meal will also be administered to Group 4 subjects.

Part 4

No standardized study meal will be administered to subjects in Part 4 of this study.

9.2 Gastrointestinal Symptoms Questionnaire

The GSQ (see Appendix H) that will be completed at the Clinical Research Center by a Part 1, Part 2, Part 3, and Part 4 subject, as well as every day at bedtime by a Part 4 subject, is being used as a separate safety monitoring tool in this study to ensure that all gastrointestinal complaints are reported by the subject. This questionnaire will include nine items (abdominal discomfort, abdominal pain, abdominal bloating, constipation, diarrhea, passing gas, belching/burping, nausea, and heartburn), each rated on a five-point Likert scale on which the lowest score, 0, denotes no symptoms and the highest score, 4, denotes the most pronounced symptoms. This questionnaire is a modified version of the "Symptoms Diary" described by Salden 2015; modifications include minor changes to medical terminology, addition of a relevant symptom (i.e., heartburn), and changes to the scale numbering (i.e., from 1-5 to 0-4).

Part 1

Each subject will complete the GSQ at Screening and pre-dose (i.e., before pretreatment buffer solution administration) on the Cohort Treatment Day to ensure that the subject is free of clinically relevant gastrointestinal symptoms. The pre-dose GSQ on the Cohort Treatment Day will be considered the baseline GSQ. The subject will complete the GSQ post-dose (i.e., after completion of study meal ingestion) at specified time points on the Cohort Treatment Day, as well as at the 24-Hour Safety Assessment, to ensure that all gastrointestinal complaints are reported by the subject.

Part 2

Each subject will complete the GSQ at Screening to ensure that the subject is free of clinically relevant gastrointestinal symptoms. The subject will complete the pre-dose GSQ (i.e., before pretreatment buffer solution administration) twice on each Cohort Treatment Day. The subject will complete the first pre-dose GSQ prior to placement of the NG tube to ensure that the subject is free of clinically relevant gastrointestinal symptoms. The subject will complete the second pre-dose GSQ after placement of the NG tube to ensure that all gastrointestinal complaints that occur in association with the placement or presence of the NG tube are reported by the subject. The post-NG tube GSQ on the Cohort Treatment Day will be considered the baseline GSQ.

The subject will complete the GSQ post-dose (i.e., after completion of study meal ingestion) at specified time points on each Cohort Treatment Day to ensure that all gastrointestinal complaints are reported by the subject.

Part 3

Each subject will complete the GSQ at Screening to ensure that the subject is free of clinically relevant gastrointestinal symptoms. The subject will complete the pre-dose GSQ (i.e., before pretreatment buffer solution administration [Group 1], before study drug administration [Group 2, Group 4, and Group 5], or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal [Group 3]) twice on each Cohort Treatment Day. The subject will complete the first pre-dose GSQ prior to placement of the NG tube to ensure that the subject is

free of clinically relevant gastrointestinal symptoms. The subject will complete the second pre-dose GSQ after placement of the NG tube to ensure that all gastrointestinal complaints that occur in association with the placement or presence of the NG tube are reported by the subject. The post-NG tube GSQ on the Cohort Treatment Day will be considered the baseline GSQ.

The subject will complete the GSQ post-dose at specified time points on each Cohort Treatment Day to ensure that all gastrointestinal complaints are reported by the subject.

Part 4

Each subject will complete the GSQ at Screening and pre-dose (i.e., before administration of the first daily dose of study drug) on Day 1 and Day 5 of each Cohort Treatment Period to ensure that the subject is free of clinically relevant gastrointestinal symptoms. The pre-dose GSQ on Day 1 of the Cohort Treatment Period will be considered the baseline GSQ.

The subject will complete the GSQ post-dose (i.e., after administration of the first daily dose of study drug) at specified time points on Day 1 of each Cohort Treatment Period to ensure that all gastrointestinal complaints are reported by the subject.

The subject will complete the GSQ every day, at bedtime, starting on Day 1 of the first Cohort Treatment Period and continuing through the day prior to the Safety Visit, to ensure that all gastrointestinal complaints are reported by the subject. The subject will complete the GSQ based on symptoms that occurred since the subject awoke that morning. The subject will be instructed to bring the GSQs (completed and not completed) to each visit at the Clinical Research Center through the Safety Visit, and study personnel will review the GSQs on Day -1 of the second Cohort Treatment Period and on Day 4 of each Cohort Treatment Period to ensure they have been completed every day.

Research staff will dispense all GSQs for the subject to complete through the Safety Visit on Day 1 of the first Cohort Treatment Period, will collect completed GSQs on Day -1 of the second Cohort Treatment Period and on Day 4 of each Cohort Treatment Period, and will collect all remaining GSQs (completed and not completed) at the Safety Visit.

9.3 Nasogastric Tube

In Part 2 and Part 3 of the study, the NG tube will be used to obtain gastric samples, as discussed in Section 9.4. Both nasal passages will be examined by the Investigator using anterior rhinoscopy to ensure their patency, and to ensure that the mucosa is normal and the septum is intact, at Screening and prior to NG tube placement on each Cohort Treatment Day. A minor septal deviation at Screening is not in itself exclusionary for study participation if, in the opinion of the Investigator, it will not preclude passage of the NG tube or pose a safety issue for the subject; however, the Investigator will pass the NG tube through the more patent nasal passage or may choose to place an OG tube instead of an NG tube.

The subject's fasting status (nothing by mouth for at least 12 hours) will be confirmed prior to placement of the NG tube. Estimation of the tube length will be performed by measuring the

distance from the tip of the nose, around the external ear (pinna), to just below the left costal margin. The tip of the tube will be cooled in ice prior to its placement to improve its rigidity to facilitate passage through the nose, and topical lidocaine gel will be applied to the tube to decrease discomfort in the nose and throat, and to reduce the gag reflex, during tube placement. If the Investigator determines that placement of an OG tube instead of an NG tube is preferable for a given subject, topical lidocaine spray may be applied to the pharynx. The topical lidocaine preparation should not contain epinephrine or PEG. The subject will be positioned sitting upright, neck partially flexed, and asked to hold a cup of 5 mL of sterile water with a straw in it and place the straw in the mouth. The physician Investigator will insert the NG tube (14-18 French size) through the nostril and along (parallel to) the floor of the nose until it reaches the back of the nose (i.e., the nasopharynx). As the tube is advanced through the throat, the subject will be asked to sip water through the straw and swallow. The subject will be asked to swallow (without water) as the tube is advanced through the upper esophagus. The tube will be advanced past the lower esophageal sphincter and into the stomach, to the predetermined length; the desired location of the NG tube tip and aspiration ports is the gastric antrum. Proper placement of the NG tube will be assessed by auscultation over the stomach during insertion of air though the tube with a syringe and by gastric pH testing. The gastric pH should be <4 to confirm proper placement of the NG tube, except on the Cohort 2C Treatment Day before which the subject will have been on a Nexium pretreatment regimen; if the Nexium pretreatment regimen results in a Cohort 2C Treatment Day gastric pH ≥4, proper placement of the NG tube will be assessed by auscultation only. The tube will be secured in place on the nose using tape. If incorrect tube placement is suspected (e.g., based on auscultation, gastric pH testing, signs, or symptoms), the tube will be completely withdrawn immediately; placement of the tube may be repeated at the discretion of the Investigator. There will be a minimum waiting period of approximately 15 minutes after NG tube placement before the next study procedure is performed.

The placement and presence of an NG tube may be associated with a variety of gastrointestinal symptoms. If a gastrointestinal sign or symptom (or other sign or symptom) occurs in association with the placement or presence of the NG tube, additional time may be allowed for it to resolve, or to lessen and be stable, such that the Investigator determines that the subject is able to continue in the study. If necessary (e.g., a symptom or sign associated with the placement or presence of the NG tube is severe) at any time during or after NG tube placement, the NG tube will be removed, and the subject will be withdrawn from the study.

A gastrointestinal symptom or sign that occurs after the NG tube is placed, but before pretreatment buffer solution administration (Part 2 and Part 3 Group 1), before study drug administration (Part 3 Group 2, Part 3 Group 4, and Part 3 Group 5), or before ingestion of the 50 mL portion of the 1 g gluten-containing study meal (Part 3 Group 3) will be considered an AE and assessed by the Investigator for relatedness to the placement or presence of the NG tube. A new gastrointestinal symptom or sign that occurs after the NG tube has been placed and the study meal has been completed (Part 2, Part 3 Group 1, Part 3 Group 2, Part 3 Group 4, and Part 3 Group 5), after the NG tube has been placed and the final portion of the study meal has been completed (Part 3 Group 3), or after the NG tube has been placed and the gluten-free study meal has been completed (Part 3 Group 4), and/or worsening of a gastrointestinal symptom or sign that occurred after placement of the NG tube by ≥1 severity grade based on CTCAE Version 4.03[1], will be

considered an AE and assessed by the Investigator for relatedness to the placement or presence of the NG tube and to the study drug.

The subject will remain in an upright (e.g., sitting) position while the NG tube is in place and for at least 15 minutes after it has been removed. The NG tube will be removed subsequent to completing all post-dose gastric sampling and prior to the ingestion of food and liquids (normal diet) ad libitum in a Part 2 Group 1 and Part 2 Group 2 subject and prior to the ingestion of plain gluten-free food and liquids in a Part 2 Group 3 and Part 3 subject (see Section 7.2.10).

9.4 Gastric Samples for pH and Gluten Degradation

In Part 2 and Part 3 of the study, the NG tube will be used to obtain gastric samples to evaluate the degradation of ingested gluten.

Immediately after the NG tube is placed on each Cohort Treatment Day, a gastric sample (approximately 5 mL) will be aspirated. A portion of this gastric sample will be tested for pH using a pH probe to confirm that the NG tube is in the stomach and to serve as the pretreatment pH measurement; a separate portion will be used for determination of gluten degradation.

Part 2

A Group 1 and Group 2 subject will be asked to move approximately 10 minutes after study drug administration and a Group 3 subject will be asked to move approximately 10 and 45 minutes after study drug administration in order to promote gastric content mixing. In addition, approximately 10, 15, and 20 minutes after study drug administration in a Group 1 and Group 2 subject and 10, 12, and 14 minutes after study drug administration in a Group 3 subject, approximately 30-40 mL of gastric contents will be gently aspirated from the NG tube using a 60 mL syringe, then reinjected through the NG tube (as described by Siegel 2012). Beginning 20 minutes (or, at most, 25 minutes) and beginning 35 minutes (or, at most, 40 minutes) after study drug administration in a Group 3 subject, a gastric sample (approximately 5 mL) will be aspirated. A portion of the approximately 5 mL gastric sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation. Beginning 35 minutes (or, at most, 40 minutes) after study drug administration in a Group 1 and Group 2 subject and 65 minutes (or, at most, 70 minutes) after study drug administration in a Group 3 subject, the entire gastric content will be aspirated and its volume will be measured. A portion of the entire gastric content sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation. The following measures may be utilized if there is an inability to aspirate gastric material (e.g., due to lack of or inaccessible gastric content, adherence of the NG tube to the gastric mucosa, blockage of the NG tube) for the pre-dose gastric sample, for the 10-, 15-, or 20-minute post-dose gastric mixing in a Group 1 or Group 2 subject, for the 10-, 12-, or 14-minute post-dose gastric mixing in a Group 3 subject, for the 35-minute post-dose gastric sample in a Group 1 or Group 2 subject, or for the 20-, 35-, or 65-minute post-dose gastric sample in a Group 3 subject: air may be inserted through the NG tube, the subject may be repositioned, or the NG tube may be repositioned (in this case, the NG tube tip and aspiration ports should still be in the gastric antrum). If necessary, the least amount

of sterile water necessary may be inserted through the NG tube and the volume of sterile water will be documented. Each gluten degradation sample will be immediately placed in a heating block at a temperature of 85 °C for 15-20 minutes to halt enzyme activity; these samples will then immediately be frozen (-80 °C ±10 °C) and subsequently shipped to a third-party contract laboratory for immunogenic gluten quantification and PEG 3350 concentration determination.

Immunogenic gluten will be quantified using enzyme-linked immunosorbent assays (ELISA) based on the commercially available monoclonal R5 and G12 antibodies that are specific for immunogenic fractions of gluten. CCI [redacted] Samples will be banked for possible future testing for gluten degradation, provided the subject consents to this.

Polyethylene glycol 3350 will be used as a marker of total gastric volume, to correct for any gastric material that may not be recovered at the 35-minute post-dose time point in a Group 1 and Group 2 subject or at the 20-, 35-, and 65-minute post-dose time point in a Group 3 subject. The PEG 3350 concentration will be determined using LC-MS/MS, and total gastric volume will be calculated by dividing the administered PEG 3350 amount by the measured PEG 3350 concentration. This will allow the total gastric gluten amount to be calculated based on total gastric volume.

Part 3

A Group 1, Group 2, or Group 5 subject will be asked to move approximately 10 minutes after study drug administration in order to promote gastric content mixing. In addition, approximately 10, 15, and 20 minutes after study administration in a Group 1, Group 2, or Group 5 subject, approximately 30-40 mL of gastric contents will be gently aspirated from the NG tube using a 60 mL syringe, then reinjected through the NG tube (as described by Siegel 2012). Beginning 35 minutes (or, at most, 40 minutes) after study drug administration in a Group 1, Group 2, or Group 5 subject, a gastric sample (approximately 15 mL) will be aspirated and its volume will be measured. A portion of the approximately 15 mL gastric sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation. Beginning 65 minutes (or, at most, 70 minutes) after study drug administration in a Group 1, Group 2, or Group 5 subject, the entire gastric content will be aspirated and its volume will be measured. A portion of the entire gastric content sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation.

A Group 3 subject will be asked to move approximately 10 minutes after study drug administration in order to promote gastric content mixing. In addition, approximately 10, 12, and 14 minutes after study administration in a Group 3 subject, approximately 30-40 mL of gastric contents will be gently aspirated from the NG tube using a 60 mL syringe, then reinjected through the NG tube (as described by Siegel 2012). Beginning 35 minutes (or, at most, 40 minutes) after study drug administration in a Group 3 subject, a gastric sample (approximately 15 mL) will be aspirated and its volume will be measured. A portion of the approximately 15 mL gastric sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation. Beginning 65 minutes (or, at most,

70 minutes) after study drug administration in a Group 3 subject, the entire gastric content will be aspirated and its volume will be measured. A portion of the entire gastric content sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation.

A Group 4 subject will be asked to move approximately 10 and 40 minutes after study drug administration in order to promote gastric content mixing. In addition, approximately 10, 12, and 14 minutes and approximately 40, 45, and 50 minutes after study administration in a Group 4 subject, approximately 30-40 mL of gastric contents will be gently aspirated from the NG tube using a 60 mL syringe, then reinjected through the NG tube (as described by Siegel 2012). Beginning 65 minutes (or, at most, 70 minutes) after study drug administration in a Group 4 subject, the entire gastric content will be aspirated and its volume will be measured. A portion of the entire gastric content sample will then be tested for pH using a pH probe; a separate portion will be used for determination of gluten degradation.

The following measures may be utilized if there is an inability to aspirate gastric material (e.g., due to lack of or inaccessible gastric content, adherence of the NG tube to the gastric mucosa, blockage of the NG tube) for the pre-dose gastric sample, for the 10-, 15-, or 20-minute post-dose gastric mixing in a Group 1, Group 2, or Group 5 subject, for the 10-, 12-, or 14-minute post-dose gastric mixing in a Group 3 or Group 4 subject, for the 40-, 45-, or 50-minute post-dose gastric mixing in a Group 4 subject, for the 35-minute post-dose gastric sample in a Group 1, Group 2, Group 3, or Group 5 subject, or for the 65-minute post-dose gastric sample in a Group 1, Group 2, Group 3, Group 4, or Group 5 subject: air may be inserted through the NG tube, the subject may be repositioned, or the NG tube may be repositioned (in this case, the NG tube tip and aspiration ports should still be in the gastric antrum). If necessary, the least amount of sterile water necessary may be inserted through the NG tube and the volume of sterile water will be documented. Each gluten degradation sample will be immediately placed in a heating block at a temperature of 85 °C for 15-20 minutes to halt enzyme activity; these samples will then immediately be frozen (-80 °C ±10 °C) and subsequently shipped to a third-party contract laboratory for immunogenic gluten quantification and PEG 3350 concentration determination.

Immunogenic gluten will be quantified using ELISA based on the commercially available monoclonal R5 and G12 antibodies that are specific for immunogenic fractions of gluten.
CCI
[redacted] Samples will be banked for possible future testing for gluten degradation, provided the subject consents to this.

Polyethylene glycol 3350 will be used as a marker of total gastric volume, to correct for any gastric material that may not be recovered at the 35-minute post-dose time point in a Group 1, Group 2, Group 3, and Group 5 subject or at the 65-minute post-dose time point in a Group 1, Group 2, Group 3, Group 4, and Group 5 subject. The PEG 3350 concentration will be determined using LC-MS/MS, and total gastric volume will be calculated by dividing the administered PEG 3350 amount by the measured PEG 3350 concentration. This will allow the total gastric gluten amount to be calculated based on total gastric volume.

9.5 Physical Examinations

A complete physical examination will be performed and will include an assessment of the following body systems: general appearance; mental status; head, eyes, ears, nose, and throat; dermatologic; cardiovascular; respiratory; gastrointestinal; musculoskeletal; and neurological. Additional body systems may be examined at the Investigator's discretion.

Part 1

The pre-dose physical examination on the Cohort Treatment Day will be considered the baseline physical examination. After study drug administration on the Cohort Treatment Day through the 24-Hour Safety Assessment, a new physical examination finding, or physical examination finding change (worsening) that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11. As noted above, the physical examination will include the gastrointestinal body system.

Part 2 and Part 3

The pre-dose physical examination on the first Cohort Treatment Day will be considered the baseline physical examination. After study drug administration on the first Cohort Treatment Day through the Safety Visit, a new physical examination finding, or a physical examination finding change (worsening) that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11. As noted above, the physical examination will include the gastrointestinal body system.

Part 4

The pre-dose (i.e., before administration of the first daily dose of study drug) physical examination on Day 1 of the first Cohort Treatment Period will be considered the baseline physical examination. After the first daily dose of study drug is administered on Day 1 of the first Cohort Treatment Period through the Safety Visit, a new physical examination finding, or a physical examination finding change (worsening) that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11. As noted above, the physical examination will include the gastrointestinal body system.

9.6 Vital Signs, Weight, and Height

Vital signs will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature and will be performed after the subject has been at rest in the seated position for at least 10 minutes. Weight will be measured using a calibrated scale with the subject wearing clothes, but no shoes. Height, which will be obtained at Screening only, will be measured using a calibrated wall mounted stadiometer with the subject's shoes off.

Part 1

The pre-dose vital signs and weight on the Cohort Treatment Day will be considered the baseline vital signs and weight. After study drug administration on the Cohort Treatment Day through the 24-Hour Safety Assessment, a new vital sign abnormality, or a vital sign change that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11.

Part 2 and Part 3

The pre-dose vital signs and weight on the first Cohort Treatment Day will be considered the baseline vital signs and weight. After study drug administration on the first Cohort Treatment Day through the Safety Visit, a new vital sign or weight abnormality, or a vital sign or weight change that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11.

Part 4

The pre-dose (i.e., before administration of the first daily dose of study drug) vital signs and weight on Day 1 of the first Cohort Treatment Period will be considered the baseline vital signs and weight. After the first daily dose of study drug is administered on Day 1 of the first Cohort Treatment Period through the Safety Visit, a new vital sign or weight abnormality, or a vital sign or weight change that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11.

9.7 Electrocardiograms

A 12-lead ECG will be obtained with the patient in a supine position following at least a 10 minute rest. The Investigator will review and report the results of each ECG; this review will include a comparison of each ECG to the baseline ECG.

Part 1

The pre-dose ECG on the Cohort Treatment Day will be considered the baseline ECG. After study drug administration on the Cohort Treatment Day through the 24-Hour Safety Assessment, a new ECG abnormality, or an ECG change that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11.

Part 2 and Part 3

The pre-dose ECG on the first Cohort Treatment Day will be considered the baseline ECG. After study drug administration on the first Cohort Treatment Day through the Safety Visit, a new ECG abnormality, or an ECG change that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11.

Part 4

The pre-dose (i.e., before administration of the first daily dose of study drug) ECG on Day 1 of the first Cohort Treatment Period will be considered the baseline ECG. After the first daily dose of study drug is administered on Day 1 of the first Cohort Treatment Period through the Safety Visit, a new ECG abnormality, or an ECG change that is assessed by the Investigator as clinically significant compared to baseline, will be considered an AE and reported as described in Section 11.

9.8 Laboratory Testing

9.8.1 Chemistry, Hematology, Urinalysis, and Other Tests

The clinical laboratory tests (chemistry, hematology, and urinalysis) that will be performed are shown in Table 10.

Table 10. Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Total bilirubin Total protein Albumin Glucose Carbon dioxide Blood urea nitrogen Creatinine Sodium Potassium Chloride	Hemoglobin Hematocrit Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Erythrocyte count Leukocyte count Neutrophil count and percentage Lymphocyte count and percentage Monocyte count and percentage Eosinophil count and percentage Basophil count and percentage Platelet count	Glucose Protein Specific gravity pH Nitrite Bilirubin Urobilinogen Ketone Blood Leukocyte esterase

Other laboratory tests will include serum and urine pregnancy tests (β-human chorionic gonadotropin) (in females), urine drug (amphetamines/methamphetamines, benzodiazepines, cannabinoids, cocaine, opiates) screen, and *Helicobacter pylori* breath test. Serum tTG IgA antibodies and total IgA will be obtained at Screening in patients with CeD.

Reports containing these laboratory test results will be generated by the laboratory performing the test. Laboratory values outside of the normal range will be assessed for clinical significance by the Investigator.

Abnormal laboratory tests may be repeated at the discretion of the Investigator or Sponsor.

Other laboratory tests may be performed by the Investigator, as deemed necessary, to evaluate, or ensure the safety of, a subject. The performance of special testing (i.e., other than the per

protocol testing performed during the study) that the Investigator deems necessary or other recommendations should be discussed in advance with the Medical Monitor or designee, if the subject's clinical status allows.

9.8.2 Blood Sampling for Pharmacokinetic Testing

Pharmacokinetic testing will be done to evaluate systemic exposure to PvP001, PvP002, and PvP003.

Blood samples will be sent to an independent laboratory for testing. Testing of these samples for PvP001, PvP002, and PvP003 will be performed using a validated method.

Part 1 and Part 2

A blood sample (approximately 5 mL) for PK testing will be obtained from each subject via an IV catheter before pretreatment buffer solution administration and approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration on the Cohort Treatment Day in Part 1 and Part 2 of the study. A blood sample for PK testing will also be obtained from each subject approximately 24 hours after study drug administration at the 24-Hour Safety Assessment in Part 1 of the study.

Part 3

A blood sample (approximately 5 mL) for PK testing will be obtained from each subject via an IV catheter before pretreatment buffer solution administration (Group 1), before study drug administration (Group 2, Group 4, and Group 5), or before ingestion of a 50 mL portion of a standardized 1 g gluten-containing study meal (Group 3), and approximately 15, 30, 45, 60, 120, 180, 240, 360, and 480 minutes after study drug administration on the Cohort Treatment Day in Part 3 of the study.

Part 4

A blood sample (approximately 5 mL) for PK testing will be obtained from each subject via an IV catheter before and approximately 15, 30, 45, 60, 120, 180, and 240 minutes after administration of the first daily dose of study drug on Day 1 and Day 5 of each Cohort Treatment Period in Part 4 of the study.

9.8.3 Blood Sampling for Anti-Drug Antibody Testing

A blood sample (approximately 5 mL) will be obtained from each subject at Screening and at the Follow Up Anti-Drug Antibody Blood Sampling Visits 14 ± 2 days and 28 ± 2 days after the Cohort Treatment Day (Part 1), after the final Cohort Treatment Day (Part 2 and Part 3), or after Day 5 of the second Cohort Treatment Period (Part 4) to test for ADA to PvP001, PvP002, and PvP003 in the serum.

Blood samples will be sent to an independent laboratory for testing. Testing of samples for ADA will be performed using validated assays. Confirmed positive samples will be further tested for

neutralizing activity. In a Part 1 and Part 2 subject who develops ADA, the ADA level will be monitored until it returns to the pre-dose baseline. In a Part 3 and Part 4 subject who develops ADA, the ADA level will be monitored monthly until it returns to the pre-dose baseline or for 6 months, whichever occurs first. As appropriate, the potential impact of ADA on safety, efficacy, and PK will be assessed.

9.8.4 Urine Sampling for Gluten Immunogenic Peptides

A urine sample will be obtained from each Part 2 Group 3 and Part 3 subject before study drug administration (i.e., before NG tube placement) and approximately 240 minutes after study drug administration. A urine sample will be obtained from each Part 4 subject before the first daily dose of study drug is administered on Day 1 and Day 5 of each Cohort Treatment Period. These urine samples will be sent to an independent laboratory to test for gluten immunogenic peptides, provided the subject consents to this. The 240-minute post-dose urine sample for gluten immunogenic peptides will be obtained prior to the ingestion of food and liquids (normal diet, which may contain gluten) ad libitum in a Part 2 Group 3 and Part 3 subject.

10 CONCOMITANT MEDICATIONS AND STUDY RESTRICTIONS

10.1 Concomitant Medications

Part 1, Part 2, Part 3, and Part 4 Healthy Adult Volunteers

Current, recent (within 7 days prior to the Screening Visit), or planned (from the Screening Visit through the Safety Follow Up Call [Part 1] or Safety Visit [Part 2, Part 3, and Part 4]) use of over-the-counter or prescription medication via any route of administration is prohibited, which includes, but is not limited to, aspirin and other nonsteroidal anti-inflammatory drugs (which may affect gastrointestinal permeability), gastric acid suppressive medications, vitamins, minerals, and herbal products. Occasional, as needed use of an over-the-counter medication during this time may be acceptable, provided it is approved by the Investigator and Medical Monitor. The exceptions are as follows:

- Hormonal contraceptive for birth control, provided it has been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit (Part 1, Part 2, Part 3, and Part 4)
- Per protocol use of Nexium before the Cohort 2C Treatment Day (Part 2); as several medications have the potential to interact with Nexium, the subject will be advised to avoid the concomitant use of other medication with Nexium
- Per protocol use of topical lidocaine (without epinephrine or PEG) on each Cohort Treatment Day (Part 2 and Part 3)
- Per protocol use of Miralax in the study meal on each Cohort Treatment Day (Part 2 and Part 3)
- At the discretion of the Investigator, IV ondansetron (e.g., lowest effective single dose) may be administered to a subject with an NG tube in place who complains of significant nausea/feeling that he or she may vomit after ingestion of the study meal on the Cohort Treatment Day (Part 2 and Part 3)

Part 1 Patients with Celiac Disease

Current, recent (within 7 days prior to the Screening Visit), or planned (from the Screening Visit through the Safety Follow Up Call) use of aspirin and other nonsteroidal anti-inflammatory drugs (which may affect gastrointestinal permeability), proton pump inhibitors, and herbal products is prohibited. Occasional, as needed use of an over-the-counter medication during this time may be acceptable, provided it is approved by the Investigator and Medical Monitor. The exceptions are as follows:

- Hormonal contraceptive for birth control, provided it has been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit

- Inhaled medication for asthma, oral and intranasal medication for allergic rhinitis, and thyroid hormone for hypothyroidism, provided they have been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit. On the Cohort Treatment Day, any dose that is usually taken by the subject in the morning and/or afternoon will not be taken, and any dose that is usually taken by the subject at night will be taken.
- Other medication that the Investigator and Medical Monitor determine will not compromise the safety of the subject or interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments), provided they have been and will be used regularly at the same dose and frequency for ≥3 months prior to the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit. On the Cohort Treatment Day, any dose that is usually taken by the subject in the morning and/or afternoon will not be taken, unless the Investigator determines, based on the subject's medical indication for use and the medication, that it should not be withheld, and any dose that is usually taken by the subject at night will be taken.
- An H_2-receptor antagonist or an antacid being used regularly at the same dose and frequency for ≥1 month prior to the Screening Visit to treat gastroesophageal reflux symptoms or disease; in this case, the gastroesophageal reflux must be stable, defined as no symptoms for ≥ 1 month prior to the Screening Visit, must be approved by the Investigator, and must not compromise the safety of the subject or interfere with or complicate study procedures or assessments (including gastrointestinal symptom or sign assessments). In addition, the medication must be able to be discontinued 48 hours prior to the Cohort Treatment Day through the 24-Hour Safety Assessment with no expected symptoms, compromise of subject safety, or interference with or complication of study procedures or assessments (including gastrointestinal symptom or sign assessments) during this period of discontinuation.

Part 1, Part 2, Part 3, and Part 4 Healthy Adult Volunteers and Part 1 Patients with CeD

After the Safety Follow Up Call (Part 1) or Safety Visit (Part 2, Part 3, and Part 4) through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit, concomitant medication will be recorded if a subject spontaneously reports an AE.

10.2 Food and Beverage Restrictions

Part 1

Each subject will fast (nothing by mouth except water) for at least 12 hours prior to the Screening clinical laboratory tests and prior to the 24-Hour Safety Assessment. Each subject will fast (nothing by mouth) for at least 12 hours prior to the Cohort Treatment Day.

Alcohol consumption is prohibited from the 72 hours prior to the Cohort Treatment Day through the 72 hours after the Cohort Treatment Day.

Each healthy subject will maintain a GFD for 24 hours prior to the Cohort Treatment Day and each patient with CeD will maintain a GFD from the Screening Visit through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit.

Part 2

Each subject will fast (nothing by mouth except water) for at least 12 hours prior to the Screening clinical laboratory tests and prior to the Safety Visit. Each subject will fast (nothing by mouth) for at least 12 hours prior to each Cohort Treatment Day.

Alcohol consumption is prohibited from the 72 hours prior to each Cohort Treatment Day through the 72 hours after each Cohort Treatment Day, as well as in the 72 hours prior to the Safety Visit.

Each Group 1, Group 2, and Group 3 subject will maintain a GFD for 24 hours prior to each Cohort Treatment Day.

On the Cohort Treatment Day, each Group 3 subject will ingest only plain gluten-free food and liquids on the list below beginning approximately 135 minutes after study drug administration (approximately 80 minutes after the NG tube has been removed) and continuing until the 240-minute post-dose urine sample for gluten immunogenic peptides has been obtained, after which the subject will ingest food and liquids (normal diet) ad libitum.

- Plain fresh uncooked fruits
- Plain fresh uncooked vegetables
- Plain hard-boiled eggs removed directly from their shells
- Plain unseasoned nuts removed directly from their shells
- Plain water
- Gatorade
- 100% fruit juice
- 100% vegetable juice

Nexium will be taken at bedtime; it should not be taken with or after food.

Part 3

Each subject will fast (nothing by mouth except water) for at least 12 hours prior to the Screening clinical laboratory tests and prior to the Safety Visit. Each subject will fast (nothing by mouth) for at least 12 hours prior to each Cohort Treatment Day.

Alcohol consumption is prohibited from the 72 hours prior to each Cohort Treatment Day through the 72 hours after each Cohort Treatment Day, as well as in the 72 hours prior to the Safety Visit.

Each Group 1, Group 2, Group 3, Group 4, and Group 5 subject will maintain a GFD for 24 hours prior to each Cohort Treatment Day.

On the Cohort Treatment Day, each subject will ingest only plain gluten-free food and liquids on the list below beginning approximately 135 minutes after study drug administration (approximately 80 minutes after the NG tube has been removed) and continuing until the 240-minute post-dose urine sample for gluten immunogenic peptides has been obtained, after which the subject will ingest food and liquids (normal diet) ad libitum.

- Plain fresh uncooked fruits
- Plain fresh uncooked vegetables
- Plain hard-boiled eggs removed directly from their shells
- Plain unseasoned nuts removed directly from their shells
- Plain water
- Gatorade
- 100% fruit juice
- 100% vegetable juice

Part 4

Each subject will fast (nothing by mouth except water) for at least 12 hours prior to the Screening clinical laboratory tests and prior to the Safety Visit. Each subject will fast (nothing by mouth except water) for at least 12 hours prior to Day 1 and Day 5 of each Cohort Treatment Period.

Alcohol consumption is prohibited from the 72 hours prior to Day 1 of the first Cohort Treatment Period through the Safety Visit.

During each Cohort Treatment Period, while admitted at the Clinical Research Center, each subject will ingest regular meals as follows:

- On Day -1 of each Cohort Treatment Period, each subject will ingest a regular meal (i.e., dinner)
- On Day 1 and Day 5 of each Cohort Treatment Period, each subject will begin to ingest a regular meal (i.e., breakfast) immediately after administration of the first daily dose of study drug
- On Day 1 and Day 5 of each Cohort Treatment Period, each subject will ingest only snack food of any type and liquids beginning approximately 135 minutes after administration of the first daily dose of study drug

- On Day 1 and Day 5 of each Cohort Treatment Period, each subject will begin to ingest a regular meal (i.e., lunch) immediately after administration of the second daily dose of study drug, approximately 255 minutes after administration of the first daily dose of study drug (i.e., after completion of the 240-minute post-dose PK sampling and clinical laboratory tests on Day 1, and after completion of the 240-minute post-dose PK sampling on Day 5)
- On Day 4 of each Cohort Treatment Period, each subject will ingest a regular meal (i.e., dinner) immediately after administration of the third daily dose of study drug by study personnel

During the remainder of each Cohort Treatment Period, when not admitted at the Clinical Research Center, each subject will self-administer study drug immediately prior to beginning the ingestion of a regular meal TID (i.e., breakfast, lunch, and dinner). Additional instructions regarding meals will be provided to each subject in the Daily PvP003 Dosing Diary (see Appendix C).

11 ADVERSE EVENTS

11.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not it is considered related to the pharmaceutical product.

A clinically significant laboratory value is an abnormal laboratory value that is accompanied by a sign or symptom; the sign or symptom (or the diagnosis when available) is considered the AE and should be recorded as such. All laboratory values, including abnormal values, will be recorded separately during the study.

A TEAE is defined as an AE with onset after pretreatment buffer solution/study drug administration or an existing condition that worsens after pretreatment buffer solution/study drug administration.

11.2 Documenting Adverse Events

All reported AEs will be documented, including events that are spontaneously reported by a subject and events that will be elicited by asking each subject a general, non-directed question such as “How are you feeling?” or “How have you been feeling since the last visit?” through the Safety Follow Up Call (Part 1) or Safety Visit (Part 2, Part 3, and Part 4). Adverse events that are spontaneously reported after the Safety Follow Up Call (Part 1) or Safety Visit (Part 2, Part 3, and Part 4) through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit will be documented. Directed questioning and examination will then be done, as appropriate.

Gastrointestinal AEs (e.g., spontaneously reported gastrointestinal symptoms or abnormal findings on abdominal physical examination) will be documented according to the above, while the GSQ is being used as a separate safety monitoring tool in this study to ensure that all gastrointestinal complaints are reported by the subject.

Whenever feasible, the AE should be documented as a medical diagnosis (highest possible level of integration). When this is not possible, the AE should be documented in terms of the sign and/or symptom observed by the Investigator or reported by the subject.

Information documented will include the description of the AE, the date of onset and the date of resolution (if applicable), severity, seriousness, relationship to study drug, relationship to study procedure (i.e., NG tube placement or presence in Part 2 and Part 3 subjects), action taken, and the outcome. It is the responsibility of the Principal Investigator to document all AEs that occur after the first dose of study drug is administered, in accordance with the guidelines above,

regardless of whether or not they are considered to be related to the study drug or to the study procedure (i.e., NG tube placement or presence in Part 2 and Part 3 subjects).

11.3 Assessment of Severity

The Investigator will categorize the **severity** of each AE according to CTCAE Version 4.03[1].

11.4 Assessment of Causality

After careful medical consideration, the Investigator will assess the **relationship** of the AE to the study drug according to the following categories:

Not related: A causal relationship between study drug and the AE can be easily ruled out (e.g., based on the temporal relationship, absence of a reasonable pathophysiologic mechanism, or direct evidence of actual cause)

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to the study drug which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to the study drug, but which could also be explained by concurrent disease or other drugs or chemicals

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to the study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals

Definitely Related: An AE that is most likely caused by the study drug, per Investigator assessment. Rechallenge is not required to fulfill this definition.

In Part 2 and Part 3 of this study, each subject will undergo placement of an NG tube. The placement and presence of an NG tube may be associated with a variety of signs and symptoms, including gastrointestinal symptoms. For this reason, the Investigator will be asked to assess each AE for relatedness to the study drug and for relatedness to the study procedure (i.e., NG tube placement or presence).

11.5 Adverse Event Outcome

The Investigator will categorize the **outcome** of each AE according to the following definitions:

Resolved: The subject recovered from the AE. Record the AE stop date.

Ongoing: At the time of the last assessment, the event is ongoing, with an undetermined outcome. (Note: An ongoing AE is not considered resolved as a result of death.) No AE stop date should be recorded when an AE is ongoing.

Chronic/Stable: At the time of last assessment, the event is ongoing and stabilized, with no change to the event outcome anticipated. Record the AE stop date.

Death: The AE directly caused death. Record the date of death as the AE stop date.

Unknown: There is an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdraws consent or is lost to follow up). No AE stop date should be recorded.

The Investigator will follow each AE until it resolves, the Investigator feels the event is stable and chronic in nature, or the subject is lost to follow up.

11.5.1 Withdrawal Due to Adverse Event

If a subject withdraws or is withdrawn by the Investigator from the study wholly or in part due to an AE, every effort must be made to follow this event until it resolves, the Investigator feels the event is stable and chronic in nature, or the subject is lost to follow up.

11.6 Breaking the Blind

Not applicable, as this study is single-blind (i.e., blinded to subject only).

12 SERIOUS ADVERSE EVENTS

12.1 Definition of Serious Adverse Events

An AE is considered serious if it results in any of the following outcomes:

- Death;
- Life-threatening;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject; and/or
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home;
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization; and
    - Development of drug dependency or drug abuse.

An AE that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious AE.

If a female subject or a female partner of a male subject becomes pregnant at any time following the first dose of study drug through the 28 ± 2 days Follow Up Anti-Drug Antibody Blood Sampling Visit, the Investigator must notify the Medical Monitor and designee within 24 hours of learning about the pregnancy. The female subject will be withdrawn from the study. Any premature terminations of pregnancy, including elective and/or spontaneous abortions, must be reported to the Medical Monitor and designee. The pregnancy will be followed to term. The status of the mother and child after delivery must be forwarded to the Medical Monitor and designee. Although pregnancy occurring in a clinical trial is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed as such. A spontaneous abortion is always considered to be an SAE.

Definition of Terms

Life-threatening: An AE is life-threatening if it places the subject at immediate risk of death from the event as it occurred (i.e., it does not include an event that, had it occurred in a more severe form, might have caused death). For example, drug induced hepatitis that resolved

without evidence of hepatic failure would not be considered life threatening, even though drug induced hepatitis can be fatal.

Hospitalization: An AE requiring hospitalization should be considered an SAE. Hospitalization scheduled for an elective procedure or treatment of a pre-existing condition that has not worsened during participation in the study (e.g., elective surgery for a pre-existing condition that has not worsened), or for a routine clinical procedure that is not the result of an AE need not be considered an SAE. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either "serious" or "non-serious" according to the defined criteria. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or in the emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Disability/incapacity: An AE is disabling or incapacitating if the event results in a substantial disruption of a subject's ability to conduct normal life functions.

12.2 Serious Adverse Event Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. If a serious unexpected AE is believed to be related to the study drug, the Sponsor will take appropriate steps to notify the Principal Investigator participating in the clinical trial of the study drug, as well as the appropriate regulatory authorities (see Section 12.5).

12.3 Reporting Serious Adverse Events

Any AE that is assessed as serious, whether or not it is related to the study drug, must be reported by the Investigator to the Medical Monitor and designee by telephone or email within 24 hours of knowledge of the event. An initial SAE report form should be filled out with the available information, even if additional information will be needed to fully document the event. All additional information relevant to the SAE must be provided to the Medical Monitor and designee within 24 hours of the Investigator's receipt of this information. Relevant medical records, including, as applicable, hospital records and autopsy reports, should be obtained by the Investigator and provided to the Medical Monitor and designee.

In the event of a fatal or life-threatening SAE, any required information for the initial report must be provided to the Medical Monitor and designee within seven calendar days of the Investigator's initial notification of the Medical Monitor and designee. For an SAE that is not fatal or life-threatening, any required information for the initial report must be provided to the Medical Monitor and designee within 15 calendar days of the Investigator's initial notification of the Medical Monitor and designee.

The Investigator will follow an SAE until it resolves, the Investigator feels the event is stable and chronic in nature, or the subject is lost to follow up. All follow up information relevant to the SAE must be provided to the Medical Monitor and designee within 24 hours of the Investigator's receipt of this information.

Instances of death, cancer, or congenital abnormality, if brought to the attention of the Investigator **AT ANY TIME** after study drug administration **AND** considered by the Investigator to be **RELATED TO THE STUDY DRUG**, must be reported to the Medical Monitor and designee.

PPD

No protocol-defined AEs for expedited reporting have been identified for this study.

12.4 Overdose

Any instance of overdose (suspected or confirmed, and irrespective of whether or not the study drug was involved) must be reported by the Investigator to the Medical Monitor and designee by telephone or email within 24 hours of knowledge of the event. An overdose with no associated signs or symptoms will not be classified as an AE or SAE, but should be reported to the Medical Monitor and designee. Any signs or symptoms of overdose should be documented as an AE or SAE (as applicable); an overdose associated with an SAE should be reported according to the procedures in Section 12.3.

In the case of an overdose, the subject will be monitored closely and managed with supportive care. Any symptoms will be treated according to the standard practices of the Investigator and the Clinical Research Center.

12.5 Safety Reporting to Regulatory Authorities

The Sponsor will prepare and submit safety reports (i.e., Investigational New Drug [IND] safety reports) to the FDA, as appropriate, in accordance with reporting requirements for SAEs. The Sponsor, or its representative, will send copies of these safety reports to the Principal Investigator. It is the responsibility of the Principal Investigator to submit this report, as well as other SAE information per the Institutional Review Board (IRB) guidelines, to the IRB.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting of SAEs, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE.

13 STUDY STOPPING CRITERIA

Part 1

Dose escalation in Part 1 of the study will proceed according to the criteria discussed in Section 4.1.

Part 2

A Group 1, Group 2, or Group 3 subject will be withdrawn from the study if one of the following individual stopping criteria is met:

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

Enrollment into Part 2 of the study will be stopped, pending further evaluation of all available safety data, if:

- 2 or more subjects meet individual subject stopping criteria
- 2 or more subjects experience a study drug-related AE of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

Part 3 and Part 4

A Part 3 or Part 4 subject will be withdrawn from the study if one of the following individual stopping criteria is met:

- The subject experiences a study drug-related SAE
- The subject experiences 2 or more study drug-related AEs of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

Enrollment into Part 3 and Part 4 of the study will be stopped, pending further evaluation of all available safety data, if:

- 2 or more subjects meet individual subject stopping criteria
- 2 or more subjects experience a study drug-related AE of Grade 2 or higher severity based on CTCAE Version 4.03[1] within the same System Organ Class

14 STATISTICS

14.1 Analysis Populations

The safety population will include all subjects who receive at least one dose of study drug. Subjects will be analyzed based on treatment received.

The intent-to-treat (ITT) population will include all subjects who receive at least one dose of study drug. In Part 2, Part 3, and Part 4 of the study, subjects will be analyzed based on the treatment to which they were randomized.

The per protocol (PP) population will include all treated subjects with no major protocol deviations. Subjects will be analyzed based on the treatment received.

Efficacy analyses will be conducted using the ITT population, with sensitivity analyses performed using the PP population.

The PK population will include all subjects who receive at least one dose of active treatment and have any PK data.

14.2 General Procedures

Categorical variables will be presented as counts and percentages within each category. Continuous variables will be summarized with number of observations, mean, standard deviation, median, and minimum and maximum values.

Part 1, Part 2, Part 3, and Part 4 analyses will be presented separately.

Part 1 analyses will be presented by dosage level of PvP001 and the MFD of PvP002. Healthy subjects and patients with CeD will be presented separately and combined.

Part 2 analyses will be presented by Group and Cohort. Select analyses will also be presented by Cohort order in each Group. Additional analyses for Part 2 Group 3 may be described in the Statistical Analysis Plan (SAP).

Part 3 analyses will be presented by Group and Cohort. Select analyses will also be presented by Cohort order in each Group.

Part 4 analyses will be presented by Cohort. Select analyses will also be presented by Cohort order.

Full details of the planned analyses will be outlined in the SAP.

14.3 Sample Size and Associated Power

No formal sample size calculations were conducted for Part 1, Part 2, or Part 4 of this study. The sample sizes in Part 1, Part 2, and Part 4 of the study were selected to meet the objectives of the

clinical trial (i.e., to assess the safety and PK of PvP001, PvP002, and PvP003 in Part 1, Part 2, and Part 4, as well as the gluten degradation ability of PvP001 and PvP002 in Part 2). In addition, in Part 2 of the study, the number of subjects in Group 1 was selected so that at least two subjects would be randomized to each of the six possible treatment orders and the number of subjects in Group 3 was selected so that at least four subjects would be randomized to each of the six possible gluten amount, PvP001 dose, and treatment order combinations; in Part 4 of the study, the number of subjects was selected so that at least three subjects would be randomized to each of the two possible treatment orders.

Sample size determination and justification were conducted only for Part 3 of this study. As residual gluten <50 mg is regarded as meaningful in reducing gluten-induced symptoms, the sample size calculation for Part 3 of the study is based on the proportion of subjects with <50 mg residual gluten. For pooled Part 3 Group 2 and Part 3 Group 3, and for Part 3 Group 5, with a sample size of 12 (i.e., six subjects in Group 2 and six subjects in Group 3), assuming the true (population) proportion is 85%, the 80% exact confidence interval (CI) will be (62%, 95%) when the observed rate is 83% (10 out of 12 subjects). Based on the width of this CI, the chosen sample size was considered to provide an acceptable level or precision in the estimation of the primary endpoint.

14.4 Efficacy Analyses

Efficacy analyses only apply to Part 2 and Part 3 of the study.

The percent of gluten degraded by PvP001 and PvP002 35 minutes after study drug administration will be calculated for each Part 2 Group 1 and Part 2 Group 2 subject for each treatment received. The percent of gluten degraded by PvP001 20, 35, and 65 minutes after study drug administration will be calculated for each Part 2 Group 3 subject for each treatment received. The percent of gluten degraded by PvP003 35 and 65 minutes after study drug administration will be calculated for each Part 3 Group 1, Part 3 Group 2, Part 3 Group 3, and Part 3 Group 5 subject for each treatment received, and the percent of gluten degraded by PvP003 65 minutes after study drug administration will be calculated for each Part 3 Group 4 subject for each treatment received. The calculation will also be performed for combined Part 3 Group 2 and Part 3 Group 3. The gluten amount recovered and the percent of gluten degraded at the scheduled time points after study drug administration will be summarized using descriptive statistics. In addition, the amount of gluten recovered in the subject's stomach after active treatment relative to the amount of gluten recovered in the same subject's stomach after placebo/comparator treatment will be reported according to the formula utilized by Siegel 2012: percent of gluten degraded = (1 – active/placebo) x 100. For Group 1, this calculation will be done for both active study drug using the MTD (Cohort 2B) and active study drug using the MTD with PPI pretreatment (Cohort 2C).

Any other efficacy analyses will be described in the SAP.

14.5 Safety Analyses

The count and percentage of subjects reporting TEAEs and TESAEs will be summarized overall, by System Organ Class, by Preferred Term within the System Organ Class, by maximum severity, and by relationship to study drug. In Part 2 and Part 3, AEs and SAEs will also be summarized by relationship to study procedure (i.e., NG tube placement or presence). All other safety parameters, including clinical laboratory values, will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables. Shift tables may be employed to present out-of-range laboratory values and abnormal ECG findings.

14.6 Pharmacokinetic Analyses

Non-compartmental PK analyses to characterize drug exposure will include, at a minimum, determination for each Cohort of maximum plasma concentration, time of maximum plasma concentration, terminal half-life, and areas under the plasma concentration-time curve (AUC) following the dose administration, derived from the plasma concentration-time data. The AUC will be estimated by the linear trapezoidal rule. Actual times at which blood samples are obtained will be used in PK analyses.

Pharmacokinetic parameters and PK concentrations will be summarized using descriptive statistics. Individual subject concentrations and mean concentrations will be presented graphically on the linear scale. Further details will be provided in the SAP.

CCI [redacted]

14.7 Interim Analyses

An interim analysis will be performed on a subset of subjects in Part 1 and Part 2 of the study.

15 ETHICS AND RESPONSIBILITIES

15.1 Good Clinical Practice

This study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (ICH E6)[4] and any applicable national and local laws and regulations (e.g., Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314). Any episode of noncompliance will be documented.

The Investigator is responsible for performing the study in accordance with this protocol and the applicable GCP guidelines, regulations, and directives, as applicable, referenced above for collecting, recording, and accurately reporting the data.

The Investigator is responsible for ensuring the privacy and data protection, per applicable requirements, as well as the health and welfare of the subjects during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The Investigator and the applicable study staff must be familiar with the requirements of the study and with the properties of the study drug described in the IB.

The Investigator at the investigational site has the overall responsibility for the conduct and administration of the study at that site and for contacts with study management, the IRB, and local authorities.

15.2 Data and Safety Monitoring Board

No Data and Safety Monitoring Board has been established for this study.

15.3 Institutional Review Board

Before initiation of the study, the Investigator must submit the protocol, IB, ICF, advertisements, and any written materials that will be made available to the subject to an IRB complying with applicable regulations and the provisions specified in the ICH guidelines for approval. Written IRB approval of the noted documents must be obtained prior to initiation of the study.

The Investigator is responsible for reporting the following to the IRB:

- All SAEs regardless of cause and whether anticipated or unanticipated (reported per IRB regulations)
- Significant findings that become known during the course of the study that might affect the willingness of subjects to continue to participate
- Protocol or consent amendments prior to the implementation of the change
- Study progress reports at least once a year, if applicable

[4] Guideline for Good Clinical Practice (GCP), ICH E6(R1) (1996).

- Notification of study completion or termination

In accordance with reporting requirements, the Investigator will also promptly report all changes in research activity and all unanticipated problems involving risk to subjects or others to the IRB. Additionally, the Investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the subject(s).

15.4 Informed Consent

Informed consent will be obtained at the Screening Visit. The Investigator or designee will thoroughly explain to the subject the purpose of the study, the associated procedures, and any expected effects and adverse reactions before any study-specific Screening procedures are conducted.

The Investigator or designee will explain that the subject is completely free to refuse participation in the study or to withdraw from the study at any time and for any reason. Similarly, the Investigator or designee will explain that the Investigator and/or Sponsor will be free to withdraw the subject at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the subject will also be explained according to current GCP guidelines (ICH E6)[4].

The subject will be provided with an ICF and will be given sufficient time and opportunity to inquire about the details of the study and to decide whether or not to participate. The subject, and the study personnel with whom the subject discusses the informed consent, will sign and date the consent form.

In the event of a change to the ICF (e.g., after a protocol amendment, if applicable), informed consent will again be obtained, and the ICF signed and dated.

15.5 Records Management and Study Monitoring

Representatives of the Sponsor may request access to all study records for inspection throughout the study or after study completion. Such access must be stated in the ICF signed by the subject.

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence and site procedures, integrity of the data, and applicable laws and/or regulations. Study monitoring will be conducted by the Sponsor or designee at regular intervals during the study and following completion of the study. Study monitors will contact the investigational site via visits to the site, telephone calls, and other communication methods in order to review the progress of the study. During the monitoring visits, the following aspects of the study conduct will be carefully reviewed: informed consent of subjects, subject recruitment, compliance with study procedures, source data verification, AE and SAE documentation and reporting, and quality of the data. The Principal Investigator must make all study data accessible to the clinical monitor, other authorized representatives of the Sponsor, members of the IRB, and regulatory inspectors. The ICF signed by the subject must indicate the possibility for review of the data by these authorized individuals/entities.

15.6 Source Documentation and Data Collection

All subject-related data will be documented in CRFs in a confidential fashion, with the subject identified by subject number and initials only. Study data will be collected using an electronic data capture system.

All the information required by the protocol must be documented and any omissions explained. The Principal Investigator must review all CRF entries for completeness and accuracy.

Source documents, including all demographic and medical information, CRFs, and the ICF for each subject in the study must be maintained by the Principal Investigator. All information in the CRFs must be traceable to the original source documents. Examples of source documents include hospital records, office visit records, physician notes, consulting physician notes, laboratory reports, study drug inventory records, subject dosing data, and diaries. Records may be written in hard copy or in an electronic medical records system. The Principal Investigator must maintain the original source document records for each subject for the length of time required by the Sponsor (see Section 15.7).

15.7 Study Files and Record Retention

All data relating to the study, including the contents of the Principal Investigator's Site Files, subject CRFs, financial records, and other source data will be stored by the Principal Investigator until written notification is received from the Sponsor indicating that records no longer require storage.

If the Principal Investigator cannot guarantee this archiving requirement at the study site, arrangements must be made between the Principal Investigator and the Sponsor to store the documents in an alternative secure facility. Study documents should not be destroyed without written approval from the Sponsor.

15.8 Auditing

Sponsor representatives may audit an investigational site to evaluate study conduct and compliance with protocols, Standard Operating Procedures, GCP, and applicable regulatory requirements. Additionally, regulatory authorities and IRB representatives may also perform audits to verify compliance with GCP guidelines. The Principal Investigator must permit these inspections as part of the study conduct.

15.9 Amendments

Protocol modifications, except those intended to reduce immediate risk to study subjects, may only be made by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB is notified in accordance with its procedures.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB, and the Principal Investigator must receive approval before implementing the change(s).

If in the judgment of the IRB, the Principal Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for a subject enrolled in the study before continued participation.

15.10 Financing and Insurance

A separate financial agreement will be made between the Principal Investigator and the Sponsor before study drug is shipped to the investigational center. Additionally, each Investigator will provide the Sponsor with financial information required to complete FDA Form 3454, as well as any additional information required for local regulatory authorities. Each Investigator will notify the Sponsor of any relevant changes in this financial information during the conduct of the study, and for 1 year after study completion.

This clinical study is insured in accordance with the corresponding local legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are damages to health and worsening of previous existing disease that would have occurred or continued if the subject had not taken part in the clinical study. The policy regarding clinical trials insurance will be provided to the investigational site by the Sponsor.

15.11 Study Report and Publications

The Sponsor is responsible for preparing a clinical study report based on the results of this study. The Sponsor’s publication policy is discussed in the Investigator's Clinical Research Agreement.

15.12 Study Discontinuation

Both the Sponsor and the Principal Investigator reserve the right to terminate the study at the Investigator’s site at any time. Should this occur, the Principal Investigator will inform the IRB of the same. In terminating the study, the Sponsor and the Principal Investigator will ensure that adequate consideration is given to the protection of the subjects’ interests.

15.13 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, and the Sponsor and its authorized representatives are allowed full access to the records. Identification of a subject in the CRF shall be by initials and Screening numbers only.

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Appendix I. Amendment 1 Summary of Changes

Rationale: Amendment 1 to the protocol includes changes to anti-drug antibody (ADA) testing time points, clarifications, and minor editorial changes.

Summary of Changes: The revisions listed below were made to Version 1 of the protocol (dated April 16, 2018) in protocol Amendment 1. (Note: Deletions are stricken and additions are indicated in bold font in the table; minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- Change to post-dose ADA testing time points to lengthen the monitoring period for development of ADA
- Change to follow up of positive ADA to assess for return to pre-dose baseline level
- Changes to duration of study participation, dose escalation, adverse event (AE) reporting, early withdrawal, inclusion and exclusion criteria, and concomitant medication use related to changes to post-dose ADA testing time points
- Allowance of ice chip ingestion before ad libitum food and liquids ingestion in Part 1 of the study
- Allowance of water during the 12-hour fasting period before the Screening Visit clinical laboratory tests (Part 1 and Part 2), 24-Hour Safety Assessment (Part 1), and Safety Visit (Part 2)
- Addition of the use of medication, if necessary, to prevent vomiting in a Part 2 subject with a nasogastric tube after study meal ingestion, and corresponding addition of intolerance, hypersensitivity, or idiosyncratic reaction to this medication to the exclusion criteria
- Allowance for additional sterile water to swallow PvP002 capsules, if necessary
- Addition of gluten-free diet confirmation on the Cohort Treatment Day
- Addition of measurement of gastric sample volume 35 minutes post-dose
- Increase in time for study meal thawing to ensure required consistency
- Addition of two references
- Name change from Agility Clinical to Precision for Medicine, Oncology and Rare Disease

Appendix J. Amendment 2 Summary of Changes

Rationale: Amendment 2 to the protocol includes changes to Inclusion Criteria for subjects with CeD and corresponding changes to Concomitant Medications; clarifications regarding the Safety 24-Hour Safety Assessment, Safety Follow Up Call, Safety Visit, and Follow Up Anti-Drug Antibody Blood Sampling Visits in subjects who do not receive study drug; and minor editorial changes.

Summary of Changes: The revisions listed below were made to Amendment 1 of the protocol (dated July 30, 2018) in protocol Amendment 2. (Note: Deletions are stricken and additions are indicated in bold font in the table; minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- Change to eligible upper age limit in patients with CeD to avoid unnecessary restrictions to eligibility of otherwise generally healthy subjects in this population
- Change to concomitant medications allowed in patients with CeD to avoid unnecessary restrictions to eligibility of otherwise generally healthy subjects in this population
- Changes to gastrointestinal tract disease, disorder, symptoms, or surgery allowed in patients with CeD to avoid unnecessary restrictions to eligibility of otherwise generally healthy subjects in this population
- Addition of confirmation of discontinuation of H_2-receptor antagonist or antacid on Cohort Treatment Day -1 and pre-dose on the Cohort Treatment Day, if applicable in patients with CeD
- Clarification of study visits for subjects who prematurely discontinue from the study
- Clarification of procedures to confirm proper placement of the nasogastric tube in a subject who has been on Nexium pretreatment
- Clarification of location of the nasogastric tube tip and aspiration ports within the stomach
- Addition of measures that may be utilized if there is an inability to aspirate gastric material
- Changes to names of drugs tested in urine drug screen to be consistent with study laboratory drug names

Appendix K. Amendment 3 Summary of Changes

Rationale: Amendment 3 to the protocol includes the addition of Group 3 to Part 2 of the study, addition of urine sample collection for possible future testing for gluten immunogenic peptides in Group 3 subjects, and minor editorial and grammatical changes.

Summary of Changes: The revisions listed below were made to Amendment 2 of the protocol (dated November 13, 2018) in protocol Amendment 3. (Note: Deletions are stricken and additions are indicated in bold font in the table; minor editorial and minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- Addition of Group 3 to Part 2 of the study to evaluate the ability of a range of PvP001 doses to degrade lower and higher gluten amounts at various time points
- Addition of urine sample collection for possible future testing for gluten immunogenic peptides in Group 3 subjects in Part 2 of the study

Appendix L. Amendment 4 Summary of Changes

Rationale: Amendment 4 to the protocol includes the addition of Part 3 and Part 4 of the study, clarifications, and minor editorial and grammatical changes.

Summary of Changes: The revisions listed below were made to Amendment 3 of the protocol (dated March 11, 2019) in protocol Amendment 4. (Note: Deletions are stricken and additions are indicated in bold font in the table; minor editorial and grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- Addition of Part 3 of the study to evaluate the ability of single doses of PvP003 to degrade 1 g of gluten in a standardized gluten-containing study meal when administered with and without pretreatment buffer solution before a standardized gluten-containing study meal, when administered between two portions of a standardized gluten-containing study meal, and when administered before a standardized gluten-free study meal followed by a standardized gluten-containing study meal, and to determine the safety, tolerability, and PK of single doses of PvP003 600 mg, in healthy volunteers
- Addition of Part 4 of the study to determine the safety, tolerability, and PK of multiple doses of PvP003 600 mg in healthy volunteers
- Change of Medical Monitor; change of eligibility question and serious adverse event reporting contacts; change of company name and address for specialty laboratory contact, PPD; and addition of specialty laboratory, Custom Biologics
- Addition of an interim analysis on a subset of subjects

Appendix M. Amendment 5 Summary of Changes

Rationale: Amendment 5 to the protocol includes the addition of Part 3 Group 5 to the study and the processing of urine samples for gluten immunogenic peptides, clarifications, and minor editorial and grammatical changes.

Summary of Changes: The revisions listed below were made to Amendment 4 of the protocol (dated January 10, 2020) in protocol Amendment 5. (Note: Deletions are stricken and additions are indicated in bold font in the table; minor editorial and grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- Addition of Part 3 Group 5 to the study to evaluate the ability of single doses of PvP003 150 mg to degrade 1 g of gluten in a standardized gluten-containing study meal and to determine the safety, tolerability, and PK of single doses of PvP003 150 mg in healthy volunteers
- Addition of specialty laboratory, Precision for Medicine, to process urine samples for gluten immunogenic peptides
- Due to the interval between parts of the study, allowance was made for healthy volunteers who participated in Part 1 or Part 2 of the study to participate in Part 3 or Part 4 of the study
- Update to PvP personnel for study-related questions and reporting

Section	Original Text	Revised Text
Sponsor Signature Page	PPD	PPD
Study Personnel and Contacts (Sponsor, Serious Adverse Event Reporting)	PPD	n/a

Appendix N. Amendment 6 Summary of Changes

Rationale: Amendment 6 to the protocol includes the revision of PvP Biologics, Inc. to Millennium Pharmaceuticals, Inc. as Millennium Pharmaceuticals, Inc. is incorporating PvP Biologics, Inc.; therefore, the sponsor name is changing from PvP Biologics, Inc. to Millennium Pharmaceuticals, Inc.

Summary of Changes: The revisions listed below were made to Amendment 5 of the protocol (dated October 18, 2020) in protocol Amendment 6. (Note: Deletions are stricken and additions are indicated in bold font in the table.)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	17-Dec-2020 13:23 UTC