Title: A randomized, double-blind, placebo-controlled study of the safety, pharmacodynamics, efficacy, and pharmacokinetics of TIMP-GLIA in subjects with well-controlled celiac disease undergoing oral gluten challenge.

NCT Number: NCT03738475

Protocol Approve Date: 10 December 2018

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.

CLINICAL TRIAL PROTOCOL

Study Title:	A randomized, double-blind, placebo-controlled study of the safety, pharmacodynamics, efficacy, and pharmacokinetics of TIMP-GLIA in subjects with well-controlled celiac disease undergoing oral gluten challenge.
Study Number:	TGLIA-5.002
Study Phase:	2a
Test Product:	TIMP-GLIA
IND Number:	17579
Indication:	Celiac Disease
Sponsor:	COUR Pharmaceuticals Development Company, INC (COUR)
Sponsor Contact:	PPD
Medical Monitor:	PPD

Version	Date
Original Protocol, v1.0	5 NOV 2018
Version 2.0	10 DEC 2018

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SPONSOR SIGNATURE PAGE

PROTOCOL TGLIA-5.002

A randomized, double-blind, placebo-controlled study of the safety, pharmacodynamics, efficacy, and pharmacokinetics of TIMP-GLIA in subjects with well-controlled celiac disease undergoing oral gluten challenge.

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

PPD

December 10, 2018

Date

December 10, 2018

Date

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TGLIA-5.002

A randomized, double-blind, placebo-controlled study of the safety, pharmacodynamics, efficacy, and pharmacokinetics of TIMP-GLIA in subjects with well-controlled celiac disease undergoing oral gluten challenge.

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Print Name:_____

Site Name:_____

SYNOPSIS

Sponsor: COUR Pharmaceuticals Development Company, Inc.

Study Title: A randomized, double-blind, placebo-controlled study of the safety, pharmacodynamics, efficacy, and pharmacokinetics of TIMP-GLIA in subjects with well-controlled celiac disease undergoing oral gluten challenge.

Test Product: TIMP-GLIA

Name of Active Ingredients: poly(lactic-co-glycolic acid) (PLGA), gliadin

Study Number: TGLIA-5.002 | **Study Phase:** 2a

Study Centers: Up to 12 centers

Primary Objective: To compare the increase from baseline in interferon-gamma (IFN-γ) spot forming units (SFUs) in a gliadin-specific enzyme-linked immunospot (ELISpot) assay after an oral gluten challenge, among patients treated with TIMP-GLIA or placebo.

Secondary Objectives:

- To compare the proportion of subjects who have a 2-fold increase (and an increase of at least 10) from baseline in IFN-γ SFUs following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To compare the change from baseline in the villus height, crypt depth, and their ratio (Vh:Cd) following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To compare the proportion of subjects who have a ≥ 0.4 decrease in Vh:Cd following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To evaluate change from baseline in the following parameters from whole blood following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo:
  - Number of intestinal intraepithelial lymphocytes (IELs)
  - Gliadin-specific T cell proliferation and cytokine secretion
  - CCI [redacted]
- To compare celiac disease (CD) signs and symptoms before and during an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To characterize the pharmacokinetics (PK) of TIMP-GLIA.
- To evaluate the safety of TIMP-GLIA.

Study Design:

This study is a randomized, double-blind, placebo-controlled clinical trial to assess the safety, pharmacodynamics, efficacy, and PK, of TIMP-GLIA in subjects with well-controlled CD following an oral gluten challenge. Subjects aged 18 to 70 years inclusive, with documented history of biopsy-proven confirmed CD, and on a gluten-free diet (GFD) for a minimum of 6 months, will be screened. Subjects who meet all inclusion and no exclusion criteria, and provide written informed consent, will be randomized within 45 days after Screening to receive 2 intravenous (IV) infusions of TIMP-GLIA, 8 mg/kg up to a maximum of 650 mg or placebo (normal saline) in a 1:1 ratio.

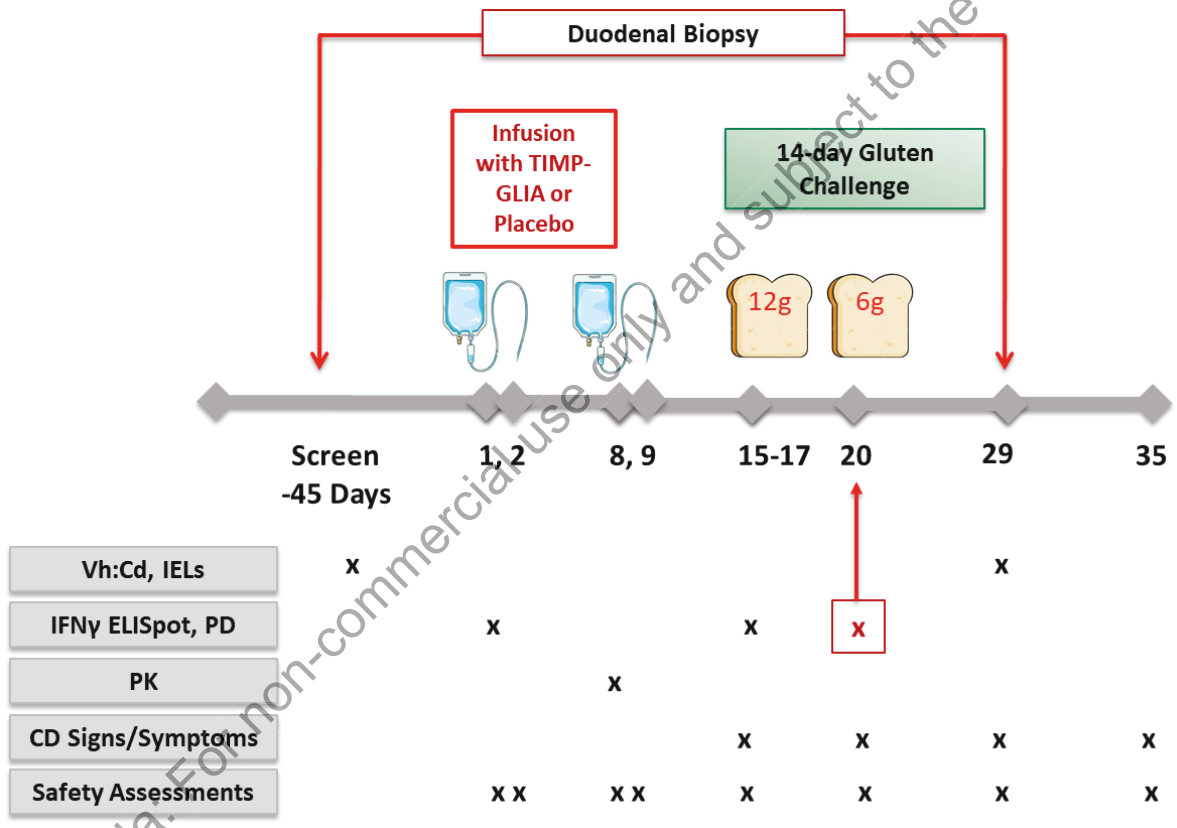
Subjects will receive TIMP-GLIA or placebo on Days 1 and 8. On Days 15 through 28, subjects will undergo a gluten challenge, by consuming 12 grams of gluten each day for 3 days, followed by 6 grams of gluten daily for 11 days. Other than the gluten challenge, subjects will continue to follow a GFD throughout the study. To ensure subjects are consuming gluten during the challenge, a urine gluten test will be performed on Days 15, 20 and 29. Subjects will be asked to complete the Celiac Symptom Index-Modified (CSI-M) questionnaire on Days 15, 20, 29, and 35.

During the Screening period and prior to the first dose on Day 1, subjects will undergo a small bowel biopsy. The biopsy will be repeated on Day 29 (-1 day). An independent, blinded pathologist will review biopsies to determine the Vh:Cd and the number of IELs.

Subjects will be observed for acute Adverse Events (AEs), including infusion reactions (IRs), for up to 2 hours following infusion on Days 1 and 8, and again for 1 hour following the first consumption of gluten on Day 15. Subjects will be assessed for safety and tolerability, including AEs, physical exam, vital signs, routine clinical lab tests (chemistry and hematology), and laboratory tests for deamidated gliadin peptide (DGP)-IgG on Days 1, 8, 15, 20, 29, and 35. Safety laboratory tests for complement levels (C3a, C5a, and SC5b-9), and serum cytokines will be performed on Days 1, 2, 8, 9, and 15. Samples for C1q binding will be performed on Days 1, 15, 20, 29, and 35.

Blood will be collected for analysis of gliadin-specific IFN-ɣ ELISpot, T cell proliferation, cytokine secretion, CCI [redacted], pre-dose on Day 1, before starting the gluten challenge on Day 15, and Day 20 (6 days after first consumption of gluten).

Blood for PK will be collected on Day 8.



Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be commissioned for this study. The DMC will be comprised of 3 physicians with expertise in CD, immunology, and interventional clinical trials. The DMC safety monitoring plan will be detailed in the DMC Charter.

Number of Subjects Planned: 30

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

1. Male or nonpregnant female, ages 18 to 70 years inclusive, at Screening Visit.
2. Biopsy-confirmed CD (intestinal histology showing villous atrophy).

3. Positive for human leukocyte antigen (HLA)-DQ2 or HLA-DQ2/DQ8 – results will be obtained at Screening if unknown or results are not available.
4. Self-reported to be on a GFD for at least 6 months prior to Screening and agree to continue GFD throughout study, with the exception of the oral gluten challenge.
5. Normal or negative celiac serology, at screening, defined as:
   a. Measurable total serum immunoglobulin A (IgA)

   AND

   b. Negative or weak positive tissue transglutaminase (tTG) IgA titer

   OR

   c. If IgA deficient, defined by a serum IgA level of < 3 mg/dL, negative or weak positive DGP-IgG titer.
6. Vh:Cd ≥ 1.5 on screening biopsy.
7. Intact spleen (no history of splenectomy or splenic disorders).
8. Willing and able to provide written informed consent.
9. Willing to perform and comply with all study procedures including attending clinic visits as scheduled, completion of the gluten challenge, and completion of biopsies.
10. Men and women of child bearing potential (WOCBP) must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, intrauterine device (IUD), or use of spermicide combined with a barrier method (e.g., condom, diaphragm) for 28 days before and after receiving the investigational product (IP).

Exclusion Criteria

1. Positive for only HLA-DQ8.
2. History of clinically confirmed immunoglobulin E (IgE)-mediated reaction and/or anaphylaxis to wheat (i.e., "wheat allergy"), barley or rye.
3. Uncontrolled CD and/or active signs/symptoms of CD, in the opinion of the investigator.
4. Untreated or active gastrointestinal disease such as peptic ulcer disease, esophagitis (Los Angeles Classification ≥ Grade C), irritable bowel syndrome, inflammatory bowel disease, or microscopic colitis.
5. Immunocompromised individuals, including those receiving immunosuppressive doses of corticosteroids (more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more within 6 months prior Dose 1, any dose of corticosteroids within 30 days of Day 1, or high dose inhaled corticosteroids [> 960 µg/day of beclomethasone dipropionate or equivalent]) or other immunosuppressive agents.
6. Type 1 diabetes.
7. Active malignancy, or history of malignancy or chemotherapy within the past 5 years other than history of localized or surgical removal of focal skin cancer, or cervical cancer in situ treated successfully in the past by local treatment (including but not limited to cryotherapy or laser therapy) or by hysterectomy.
8. Pregnant or nursing women.
9. Current infection with human immunodeficiency virus (HIV) or hepatitis B or C virus.
10. Any acute illness including, fever (>100.4°F or >38°C) within 14 days of Day 1.

11. Clinically significant abnormality on electrocardiogram (ECG).
12. Clinically significant serum chemistry or hematology abnormalities ≥ Grade 2 (Appendix 2, Toxicity Grading Scale).
13. Other active comorbidities that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the study requirements.
14. Changes to medication used to manage an underlying comorbidity within 60 days prior Day 1.
15. Known allergy to PLGA, sucrose, or mannitol.
16. Receipt of TIMP-GLIA in prior clinical trial.
17. Receipt of any investigational drug within 28 days or 5 half-lives prior to Day 1.
18. Receipt of a live vaccine within 28 days prior or a subunit vaccine within 14 days prior to Day 1or planned vaccination prior to Day 35.
19. Donation of blood or plasma within 56 days prior to Day 1.
20. Receipt of blood products, monoclonal antibody, or other systemic protein therapy within 6 months prior to Day 1. NOTE: oral protein supplements are permitted.
21. Participation in an oral gluten challenge within 6 months prior to Day 1.
22. History of drug or alcohol abuse that, in the opinion of the Investigator, would interfere with the subject's ability to comply with the study requirements.
23. Any other condition that, in the opinion of the Investigator would make the subject unsuitable for the study or unable to comply with the study requirements.

Duration of Treatment: 2 doses, 7 days apart. The total duration for subject participation is ~78 days: up to 45 day Screening period, followed by 35 days on study.

Test Product; Dose; and Mode of Administration: TIMP-GLIA 8 mg/kg up to a maximum of 650 mg; administered by IV infusion.

Reference Therapy; Dose; and Mode of Administration: Normal saline, administered by IV infusion.

Criteria for Evaluation:

Pharmacodynamics:

- IFN- ɣ SFUs in a gliadin-specific ELISpot
- Gliadin-specific T cell proliferation and cytokine secretion by ELISA
- CCI [redacted]

Histology:

- Villus height, crypt depth, and Vh:Cd
- Number of IELs

CD Signs and Symptoms:

- Responses to CSI-M (Appendix 3)

PK:

- Maximal observed concentration (C_{max})
- Time of maximal observed concentration (T_{max})
- Area under the concentration-time curve (AUC) from time zero and extrapolated to infinity (AUC_{inf})
- AUC from time zero to time of the last measurable concentration (AUC_{last})

Safety:

- AEs and serious AEs (SAEs) (clinically significant abnormal physical exam findings and laboratory results will be reported as AEs)
- Vital signs
- Serum chemistries and hematology
- DGP-IgG antibodies
- Serum complement levels: C1q binding, C3a, C5a, SC5B-9
- Serum cytokines: IFN-gamma, IL1-beta, IL-2, IL-4, IL-6, IL-8 , IL-10, IL-12p70, TNF-alpha

Statistical Methods:

Sample Size: For the primary efficacy endpoint, using a 2-sided 0.05 significance level, a statistical power of ~70%, and assuming an increase in mean IFN- ɣ SFUs in the placebo group of 75 (standard deviation [SD] 100) and in the TIMP-GLIA group of 5 (SD 10), 15 subjects per group will allow detection of a difference of 70 in mean reductions in SFUs between the TIMP-GLIA and placebo groups.

An interim analysis will be performed when Day 29 data are available for the 30 subjects. The final sample size will be determined based on the operating characteristics for a decision criterion using a Bayesian approach. An additional 20 subjects (10 per arm) may be randomized based on the interim results.

Analyses:

Efficacy/Pharmacodynamics:

The mean changes from baseline in IFN-γ SFUs within and between treatment groups will be compared using a Wilcoxon Signed Rank Test and a Wilcoxon Rank Sum Test, respectively.

The proportion of subjects with a 2-fold increase (and an increase of at least 10) in IFN-γ SFUs in the placebo and TIMP-GLIA groups will be compared using a Fisher's Exact Test.

The mean changes from baseline in villus height, crypt depth, and their ratio (Vh:Cd) within and between treatment groups will be compared using a Wilcoxon Signed Rank Test and a Wilcoxon Rank Sum Test, respectively.

The proportion of subjects with a decrease of ≥ 0.4 in Vh:Cd in the placebo and TIMP-GLIA groups will be compared using a Fisher's Exact Test.

The mean changes from baseline in IELs within and between treatment groups will be compared using a Wilcoxon Signed Rank Test and a Wilcoxon Rank Sum Test, respectively.

Descriptive statistics will be used to summarize all other pharmacodynamic endpoints.

Subject responses to the CSI-M will be summarized using descriptive statistics.

PK:

Individual subject TIMP-GLIA concentrations and derived PK parameters will be summarized using descriptive statistics.

Safety:

Frequencies and percentages of subjects with AEs and SAEs will be summarized by treatment group. Safety labs and vital signs data will be summarized with descriptive statistics by treatment group.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Aalkaline phosphatase
APCs	Antigen-Presenting Cells
AST	Aspartate Aminotransferase
CD	Celiac Disease
CSI-M	Celiac Symptom Index-Modified
CO_2	Carbon Dioxide/Bicarbonate
CFR	Code of Federal Regulations
DGP-IgG	Deamidated gliadin peptide immunoglobulin G
DMC	Data Monitoring Committee
DTH	Delayed-type hypersensitivity
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot assay
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFD	Gluten-free diet
CFR	Code of Federal Regulations
GLP	Good Laboratory Practice
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IgA	Immunoglobulin A
IgE	Immunoglobulin E
ICF	Informed consent form
IR	Infusion reaction
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
ICH-GCP	International Conference of Harmonisation-Good Clinical Practice
INR	International normalized ratio
IFN-γ	Interferon-gamma
IL-15	Interleukin-15
IV	Intravenous
IUD	Intrauterine device
IP	Investigational Product

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Affairs
MHC	Major histocompatibility complex
NOAEL	No observed adverse effect level
PBMC	Peripheral blood mononuclear cells
PLGA	Poly(DL-lactide-coglycolide)
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SFUs	Spot forming units
TIMP	Tolerogenic Immune Modifying Particles
TIMP-GLIA	Tolerogenic Immune Modifying Particles - Gliadin
TBL	Total bilirubin
tTG-IgA	Tissue transglutaminase immunoglobulin A
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of child bearing potential

1 INTRODUCTION

1.1 Background on Indication

Celiac disease (CD) is an autoimmune disorder involving both an innate and adaptive immune response that occurs among genetically predisposed subjects who are exposed to gluten-containing foods and other environmental factors (Green 2016). The prevalence of CD in the United States is ~0.7%, similar to that found in several European countries (Rubio-Tapia 2012).

CD develops in genetically predisposed subjects as a consequence of an abnormal inflammatory T cell response to dietary prolamin protein, predominately gliadin, which becomes deamidated by tissue transglutaminase in the intestine. When deamidated gliadin-specific CD4+ T cells recognize their cognate gliadin epitope presented by human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 on antigen-presenting cells (APCs) in the lamina propria, they become activated and produce proinflammatory cytokines such as interferon-gamma (IFN-γ). This triggers an inflammatory cascade resulting in crypt hyperplasia and villous flattening characteristic of CD biopsy findings. Within the intestinal epithelium gliadin also triggers local production of interleukin-15 (IL-15) by enterocytes. This IL-15 increases expression of major histocompatibility complex (MHC) class I surface antigens (such as MHC class I polypeptide-related sequence A) on epithelial cells and also increases expression of corresponding MHC receptors (such as NKG2D) on intraepithelial T cells (i.e., CD8+αβ T cells and γδ T cells, natural killer [NK] cells), leading to epithelial cell destruction (Fasano 2012; Green 2007; Mazzarela 2008; Schuppan 2009).

Classic intestinal symptoms of CD include diarrhea, malnutrition, or a malabsorption syndrome (indicated by weight loss, steatorrhea, and edema secondary to hypoalbuminemia) (Ludvigsson 2013). Extraintestinal symptoms include osteoporosis, anemia, and dermatitis herpetiformis. Less than 50% of adults present with classical intestinal symptoms (Fasano 2003; Green 2001).

1.2 Limitations of Current Treatments

Gluten avoidance by dietary modification, the "gluten-free" diet (GFD), is the only effective treatment for CD as there are currently no medications that can reliably and safely prevent the mucosal damage caused by exposure to gluten. While the GFD has been shown to alleviate many of the symptoms of disease, strict adherence is difficult, and creates an additional burden on the day-to-day functioning of the celiac patient. In reality, the complete elimination of gluten from the diet is not realistic and repeated gluten exposure, albeit unintentional or in small amounts, prevents complete recovery of symptoms and repair of intestinal damage (Laurin 2002; Leffler 2017; Rubio-Tapia 2013).

Therapeutic approaches rendering T cells tolerant to gluten could potentially cure CD, thus eliminating the burdens associated with lifetime GFD and co-morbidities associated with the disease such as cancer. There are no Food and Drug Administration (FDA) approved treatments for CD in the US.

1.3 TIMP-GLIA

COUR is developing Tolerogenic Immune Modifying Particles (TIMP) - Gliadin (TIMP-GLIA) as a first-in-class, non-immunosuppressive agent to specifically inactivate, or tolerize, gliadin-specific T cells, thereby abrogating and/or reversing the underlying pathology of CD.

TIMP-GLIA is comprised of gliadin extract drug substance within a negatively charged polymer matrix of poly(DL-lactide-coglycolide (PLGA) particles. TIMP-GLIA delivers the gliadin antigen via natural phagocytosis of the PLGA particles to APCs in a noninflammatory process. Negatively charged particles delivered intravenously leads to antigen presentation of the gliadin in the spleen and liver by APCs. Gliadin-specific T cells are likely tolerized by at least one of the following mechanisms: they become anergic, are deleted, or switch to T regulatory cells. As a result of tolerance, the deleterious immune cascade is minimized or eliminated in response to gliadin. TIMP-GLIA is designed and directed to specifically address and limit the T cell response that drives CD (Getts 2015).

1.4 Nonclinical Pharmacology and Toxicology Studies

Summaries of the nonclinical pharmacology and toxicology studies are provided below. Additional details of the studies can be found in the current Investigator Brochure.

1.4.1 Nonclinical Models of Antigen-Specific Immune Tolerance

In Vivo Pharmacology - Mice

In vivo pharmacology studies to demonstrate the ability of TIMP-GLIA (compared to controls) to induce antigen-specific tolerance were performed in 3 mouse models:

Table 1 Mouse Models of Immune Tolerance

Model	Objectives	Measures
Prophylaxis (active priming)	Demonstrate antigen-specific tolerance	Ear swelling (delayed-type hypersensitivity [DTH]) Anti-gliadin antibody Ex-vivo splenic T cell proliferation, inflammatory cytokine secretion
Gliadin-induced intestinal autoimmunity (adoptive transfer of splenocytes)	Demonstrate reversal or prevention of intestinal pathology	Weight loss Severity of histological duodenitis Ex-vivo splenic inflammatory cytokine secretion
Transgenic mouse expressing celiac associated HLA DQ8 / huCD4	Demonstrate antigen-specific tolerance in the context of HLA-DQ8	Anti-gliadin antibody Ex-vivo splenic inflammatory cytokine secretion

In each model, mice received intravenous (IV) doses of TIMP-GLIA, up to 125 mg/kg (human equivalent dose [HED] ~10 mg/kg), administered 7 days apart.

In the prophylaxis and transgenic mouse models, treatment with TIMP-GLIA reduced the immune response as measured by: reduction in anti-gliadin antibodies, and reduction in activation of ex vivo gliadin-specific splenic T cells measured by proliferation and inflammatory cytokines, including IFN-γ, compared to the control group. In the prophylaxis model, treatment with TIMP-GLIA reduced DTH (ear swelling) compared to the control group.

In the gliadin-induced intestinal autoimmunity model, treatment with TIMP-GLIA prevented weight loss, reduced the severity of duodenitis, and reduced secretion of ex vivo splenic gliadin-specific inflammatory cytokines compared to control group. The outcomes for mice treated with TIMP-GLIA were similar to those of mice receiving a GFD.

TIMP-GLIA induced gliadin-specific immune tolerance in each model. Additionally, TIMP-GLIA was not associated with adverse events (AEs) or immune activation.

Ex Vivo Pharmacology - Human-Donor Peripheral Blood Mononuclear Cells

Peripheral blood (from which peripheral blood mononuclear cells [PBMCs] were harvested) was collected from healthy donors, donors with CD adhering to a GFD, and newly diagnosed celiac donors not on a GFD. TIMP-GLIA incubation with PBMCs from these patients at concentrations as high as 1.25 mg/mL (HED 100 mg/kg) did not cause T cell proliferation or inflammatory cytokine production.

1.4.2 Pharmacokinetics

Pharmacokinetic study results in repeat dose toxicology studies in rats suggest that the pharmacokinetics of plasma gliadin (measured via enzyme-linked immunosorbent assay [ELISA]) is similar on Days 1 and 8 and that the kinetics are similar in male and female rats. Maximum plasma gliadin concentrations (C_{max}) occurred rapidly and declined in an apparent biphasic manner with plasma concentration declining relatively rapidly over the first 1 to 4 hours. The time to reach the lower limit of quantitation varied but in general, plasma concentrations were below the lower limit of quantification (0.25 µg/mL for plasma gliadin) within 24 hours. C_{max} increased with increasing dose. The area under the concentration versus time curve from the start of dose administration to the last observed quantifiable concentration ($AUC_{(0\text{-}t)}$) also increased with increasing dose. Half-life estimates across doses and genders were similar and ranged from 5.4 to 6.8 hours.

1.4.3 Toxicology

Three repeat-dose toxicology studies of TIMP-GLIA were conducted in rats. Two studies were non-Good Laboratory Practice (GLP) dose range finding studies; the third study was a GLP study. In the non-GLP studies, TIMP-GLIA was administered by IV bolus on 2 days (Days 1 and 8, and Days 1 and 5). In the GLP study, TIMP-GLIA was administered by IV bolus on Days 1, 8, and 15.

In the GLP study, all animals survived until the scheduled necropsy and remained in good health throughout the course of the study. There were no significant abnormal clinical findings during the study and no drug-related effects were noted on body weight, body weight gain, food consumption, ophthalmology exams, physical exams, clinical observations, functional

observational battery, body temperature and serum cytokine levels. The results of the microscopic evaluation of the tissues obtained at necropsy of the animals terminated on Day 16 or Day 43 from each sex and dose group did not exhibit any pathologically significant findings. One animal treated with 75 mg/kg and euthanized on Day 16 (rat number 5011) had a +2 liver necrosis but this was considered by the board-certified pathologist to be within the background for Sprague Dawley rats. There was some evidence of local hemorrhage and inflammation at the tail vein injection site, but these were restricted to the immediate region of the injection (with no evidence of similar changes in any other tissues examined), occurred in control animals, and were considered to be typical results from an IV injection. The no observed adverse effect level (NOAEL) from this pivotal GLP toxicology study in rats was determined to be 75 mg/kg.

Because the NOAEL (75 mg/kg) occurred at the maximum dose in the GLP toxicology study, a small follow up study was performed to evaluate 2 doses of TIMP-GLIA at 100 and 150 mg/kg, administered by IV bolus. All animals survived until euthanasia for necropsy and no abnormal clinical behaviors were observed. TIMP-GLIA-related effects were noted on clinical chemistry and hematology tests and generally were mild or moderate. IV bolus administration of TIMP-GLIA to rats at 100 or 150 mg/kg on Day 1 and 5 was associated with liver and spleen effects. The primary effect in the liver and spleen was infiltration of monocytes/macrophages which was considered to be potentially consistent with infusion of highly concentrated nanoparticles. A no-effect level was not determined in this study.

1.5 Clinical Trials of TIMP-GLIA

Study TGLIA-5.001 is a Phase 1 study designed to evaluate the safety and tolerability of single and multiple ascending doses of TIMP-GLIA in subjects aged 18 to 75 with biopsy proven CD. Single doses range from 0.1 to 8 mg/kg of TIMP-GLIA (Part A); repeat doses of TIMP-GLIA include 2, 4, and 8 mg/kg (Part B).

Dosing in Part A is complete and all subjects have a minimum of 16 weeks follow-up (as of December 10, 2018). A total of 17 subjects were enrolled sequentially into Part A of the study. Two subjects each received doses of 0.1 and 0.5 mg/kg; 3 subjects each received doses of 1, 2, and 4 mg/kg; and 4 subjects received 8 mg/kg. At total of 6 subjects were enrolled sequentially into Part B of the study. Two subjects each received 2 doses of 2 mg/kg, 4 mg/kg, and 8 mg/kg. Twelve subjects in Part A have completed the study. The remaining subjects will be followed for safety through Day 180.

During Part A of the study, 2 of the 4 subjects who received a single 8 mg/kg dose experienced a mild to moderate infusion reaction (IR). The first subject developed a rash (grade 2), systolic hypotension (grade 2), and concentration disturbance (grade 1) at ~5 minutes into the infusion. The investigator discontinued the infusion and the symptoms resolved within minutes. The second subject experienced flushing (grade 2), nausea (grade 1), vomiting (grade 1), back pain (grade 1), and visual changes (grade 1). The onset of symptoms occurred within the first few minutes of the infusion. The investigator stopped the infusion and the symptoms resolved. The investigator subsequently treated the subject with IV diphenhydramine, 12.5 mg, and restarted the infusion per protocol at 25% of the original rate, increasing to 50% of the original rate, and then to the full rate at 15 minute intervals. The subject completed the infusion without further incident.

Upon review of all safety data, an independent Data Monitoring Committee (DMC) recommended that 1) the IP be diluted in 200 mL of normal saline (originally 100 mL), and 2) the IP be infused over ~2.5 hours - 20mL/hour for the first 15 minutes, 40 mL/hour for the next 15 minutes, and then 80 mL/hour for the duration of the infusion (originally the drug was infused at a constant rate over 30 minutes).

During Part B of the study, 1 subject (of 2) receiving 4 mg/kg experienced mild back pain during both infusions at ~10 minutes into the infusion. The investigator briefly interrupted the first infusion and did not interrupt the second infusion. There were no other AEs reported in any of the other 5 subjects receiving a repeat dose of TIMP-GLIA

There were no serious AEs (SAEs) reported in any subject in Part A or Part B to date. All but 1 AE were ≤ grade 2 (moderate); 1 subject reported grade 3 (non-celiac) colitis that the investigator deemed not related to TIMP-GLIA. The most frequent events observed in ≥ 2 subjects include: flushing (n=5, 22%), headache (n=4, 17%), back pain (n=3, 13%), fatigue (n=2, 9%), abdominal pain (n=2, 9%), and diarrhea (n=2, 9%). Flushing was only observed in the single dose subjects. Two subjects in Part A experienced back pain (1 at 4 mg/kg, 1 at 8 mg/kg) compared to 1 subject (4 mg/kg) in the repeat dose group. There was no trend for any other AE.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To compare the increase from baseline in IFN-γ spot forming units (SFUs) in a gliadin-specific enzyme-linked immunospot (ELISpot) assay after an oral gluten challenge, among patients treated with TIMP-GLIA or placebo.

2.1.2 Secondary Objectives

- To compare the proportion of subjects who have a 2-fold increase (and an increase of at least 10) from baseline in IFN-γ SFUs following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To compare the change from baseline in the villus height, crypt depth, and their ratio (Vh:Cd) following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To compare the proportion of subjects who have a ≥ 0.4 decrease in Vh:Cd following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To evaluate change from baseline in the following parameters from whole blood following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo:
  - Number of intestinal intraepithelial lymphocytes (IELs)
  - Gliadin-specific T cell proliferation and cytokine secretion
  - CCI [redacted]
- To characterize the pharmacokinetics (PK) of TIMP-GLIA.
- To compare CD signs and symptoms before and during an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.
- To evaluate the safety of TIMP-GLIA.

2.2 Endpoints

2.2.1 Pharmacodynamic Endpoints

- IFN- γ SFUs in a gliadin-specific ELISpot
- Gliadin-specific T cell proliferation and cytokine secretion by ELISA
- CCI [redacted]

2.2.2 Histology Endpoints

- Villus height, crypt depth, and Vh:Cd
- Number of IELs

2.2.3 CD Signs and Symptoms:

- Responses to Celiac Symptom Index-Modified (CSI-M, Appendix 3)

2.2.4 Pharmacokinetic Endpoints

- Maximal observed concentration (C_{max})
- Time of maximal observed concentration (T_{max})
- Area under the concentration-time curve (AUC) from time zero and extrapolated to infinity (AUC_{inf})
- AUC from time zero to time of the last measurable concentration (AUC_{last})

2.2.5 Safety Endpoints

- AEs and SAEs (clinically significant abnormal physical exam findings and laboratory results will be reported as AEs)
- Vital signs
- Serum chemistries and hematology
- DGP-IgG antibodies
- Serum complement levels: C1q binding, C3a, C5a, SC5B-9
- Serum cytokines: IFN-gamma, IL1-beta, IL-2, IL-4, IL-6, IL-8 , IL-10, IL-12p70, TNF-alpha

3 STUDY DESIGN

3.1 Overall Study Design

This study is a randomized, double-blind, placebo-controlled clinical trial to assess the safety, pharmacodynamics, efficacy, and PK, of TIMP-GLIA in subjects with well-controlled CD following an oral gluten challenge. Subjects aged 18 to 70 years inclusive, with documented history of biopsy-proven confirmed CD, and on a GFD for a minimum of 6 months, will be screened. Subjects who meet all inclusion and no exclusion criteria, and provide written informed consent, will be randomized within 45 days after Screening to receive 2 IV infusions of TIMP-GLIA, 8 mg/kg up to a maximum of 650 mg or placebo (normal saline) in a 1:1 ratio.

Subjects will receive TIMP-GLIA or placebo on Days 1 and 8. On Days 15 through 28, subjects will undergo a gluten challenge, by consuming 12 grams of gluten each day for 3 days, followed by 6 grams of gluten daily for 11 days. Other than the gluten challenge, subjects will continue to follow a GFD throughout the study. To ensure subjects are consuming gluten during the challenge, a urine gluten test will be performed on Days 15, 20 and 29. Subjects will be asked to complete the CSI-M questionnaire on Days 15, 20, 29, and 35.

During the Screening period and prior to the first dose on Day 1, subjects will undergo a small bowel biopsy. The biopsy will be repeated on Day 29 (-1 day). An independent, blinded pathologist will review biopsies to determine the Vh:Cd and the number of IELs.

Subjects will be observed for acute AEs, including IRs, for up to 2 hours following infusion on Days 1 and 8, and again for 1 hour following the first consumption of gluten on Day 15. Subjects will be assessed for safety and tolerability, including AEs, physical exam, vital signs, routine clinical lab tests (chemistry and hematology), and laboratory tests for DGP-IgG on Days 1, 8, 15, 20, 29, and 35. Safety laboratory tests for complement levels (C3a, C5a, and SC5b-9), and serum cytokines will be performed on Days 1, 2, 8, 9, and 15. Samples for C1q binding will be performed on Days 1, 15, 20, 29, and 35.

Blood will be collected for analysis of gliadin-specific IFN-γ ELISpot, T cell proliferation, cytokine secretion, CCI [redacted] pre-dose on Day 1, before starting the gluten challenge on Day 15, and Day 20 (6 days after first consumption of gluten).

Blood for PK will be collected on Day 8.

3.2 Rationale for Study Design

3.2.1 General Design Issues

This is a proof of concept study designed to evaluate the pharmacodynamics and efficacy of TIMP-GLIA. An oral gluten challenge in subjects who have been on a GFD and are asymptomatic has been shown to induce immune responses in blood (e.g., IFN-γ SFUs) and histological changes (e.g., decrease in Vh:Cd) on small bowel biopsy. Subjects enrolled in this study will be evaluated for immune responses and histological changes following 2 doses of TIMP-GLIA or placebo and a 14-day gluten challenge.

3.2.2 Selection of Population

The study population consists of patients with biopsy-confirmed, asymptomatic CD and following a GFD. This study population reflects a population most likely to respond to a gluten challenge.

3.2.3 Selection of Dose

In the Phase 1 study (Section 1.5) the TIMP-GLIA dose of 8 mg/kg up to a maximum of 650 mg was the highest dose tolerated, thus will be evaluated for pharmacodynamics and efficacy in this study.

3.3 Date Monitoring Committee

An independent DMC will be commissioned for this study. The DMC will be comprised of 3 physicians with expertise in CD, immunology, and interventional clinical trials. The DMC safety monitoring plan will be detailed in the DMC Charter.

The primary responsibility of the DMC is to safeguard study subjects by reviewing and assessing the clinical safety data being collected during the performance of the study. The DMC will review SAEs (Section 7.2.2) and ≥ Grade 3 AEs that are "Likely" (Section 7.2.3) to be related to IP as these events may occur. They will also meet periodically throughout the study to review cumulative safety data.

Based on these evaluations of the data, the DMC will make recommendations to the Sponsor to continue the study as planned, or to modify, temporarily suspend, or terminate the study. The DMC will also be responsible for identifying issues and making recommendations regarding the monitoring of subjects for safety, including collection of additional safety data.

The Sponsor will be responsible for notifying Investigators and Regulatory Authorities of any DMC recommendations, as appropriate.

3.4 Subject Participation and Study Duration

The total duration of enrollment is estimated to be 3-4 months. The duration of each subject's participation (including Screening) is approximately 78 days (11 weeks). Thus, the study is expected to last approximately 7 months.

4 SUBJECT POPULATION

Approximately 30 subjects who meet the eligibility criteria will be enrolled.

4.1 Inclusion Criteria

1. Male or nonpregnant female, ages 18 to 70 years inclusive, at Screening Visit.
2. Biopsy-confirmed CD (intestinal histology showing villous atrophy).
3. Positive for HLA-DQ2 or HLA-DQ2/DQ8 – results will be obtained at Screening if unknown or results are not available.
4. Self-reported to be on a GFD for at least 6 months prior to Screening and agree to continue GFD throughout study, with the exception of the oral gluten challenge.
5. Normal or negative celiac serology, at screening, defined as:

    a. Measurable total serum immunoglobulin A (IgA)

    AND

    b. Negative or weak positive tissue transglutaminase (tTG) IgA titer

    OR

    c. If IgA deficient, defined by a serum IgA level of < 3 mg/dL, negative or weak positive DGP IgG titer.

6. Vh:Cd ≥ 1.5 on screening biopsy.
7. Intact spleen (no history of splenectomy or splenic disorders).
8. Willing and able to provide written informed consent
9. Willing to perform and comply with all study procedures including attending clinic visits as scheduled, completion of the gluten challenge, and completion of the biopsies.
10. Men and women of child bearing potential (WOCBP) must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, intrauterine device (IUD), or use of spermicide combined with a barrier method (e.g., condom, diaphragm) for 28 days before and after receiving the investigational product (IP).

4.2 Exclusion Criteria

1. Positive for only HLA-DQ8.

2. History of clinically confirmed immunoglobulin E (IgE)-mediated reaction and/or anaphylaxis to wheat (i.e., "wheat allergy"), barley or rye.

3. Uncontrolled CD and/or active signs/symptoms of CD, in the opinion of the investigator.

4. Untreated or active gastrointestinal disease such as peptic ulcer disease, esophagitis (Los Angeles Classification ≥ Grade C), irritable bowel syndrome, inflammatory bowel disease, or microscopic colitis.

5. Immunocompromised individuals, including those receiving immunosuppressive doses of corticosteroids (more than 20 mg of prednisone given daily or on alternative days for 2 weeks or more within 6 months prior Dose 1, any dose of corticosteroids within 30 days of Day 1, or high dose inhaled corticosteroids [> 960 µg/day of beclomethasone dipropionate or equivalent]) or other immunosuppressive agents.

6. Type 1 diabetes.

7. Active malignancy, or history of malignancy or chemotherapy within the past 5 years other than history of localized or surgical removal of focal skin cancer, or cervical cancer in situ treated successfully in the past by local treatment (including but not limited to cryotherapy or laser therapy) or by hysterectomy.

8. Pregnant or nursing women.

9. Current infection with human immunodeficiency virus (HIV) or hepatitis B or C virus.

10. Any acute illness including, fever (>100.4°F or >38°C) within 14 days of Day 1.

11. Clinically significant abnormality on electrocardiogram (ECG).

12. Clinically significant serum chemistry or hematology abnormalities ≥ Grade 2 (Appendix 2, Toxicity Grading Scale).

13. Other active comorbidities that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the study requirements.

14. Changes to medication used to manage an underlying comorbidity within 60 days prior Day 1.

15. Known allergy to PLGA, sucrose, or mannitol.

16. Receipt of TIMP-GLIA in prior clinical trial.

17. Receipt of any investigational drug within 28 days or 5 half-lives prior to Day 1.

18. Receipt of a live vaccine within 28 days prior or a subunit vaccine within 14 days prior to Day 1 or planned vaccination prior to Day 35.

19. Donation of blood or plasma within 56 days prior to Day 1.

20. Receipt of blood products, monoclonal antibody, or other systemic protein therapy within 6 months prior to Day 1. NOTE: oral protein supplements are permitted.

21. Participation in an oral gluten challenge within 6 months prior to Day 1.

22. History of drug or alcohol abuse that, in the opinion of the Investigator, would interfere with the subject's ability to comply with the study requirements.

23. Any other condition that, in the opinion of the Investigator would make the subject unsuitable for the study or unable to comply with the study requirements.

4.3 Subject and Study Discontinuation

A clear distinction will be made between subjects who are withdrawn from dosing and those who prematurely discontinue from the study. **Only those subjects who withdraw consent or refuse any further contact with respect to the study will be discontinued from the study**. Subjects withdrawn from dosing will be encouraged to remain on the study for safety follow-up and have clinic visits/telephone calls in accordance with the Schedule of Events (Appendix 1).

4.3.1 Screening Failures

Subjects who sign and date the informed consent form (ICF) but who fail to meet the inclusion and exclusion criteria are defined as screen failures. A screening log, which documents the subject's initials and reason(s) for screen failure, is to be maintained for all screen failures. A copy of the log should be retained in the Investigator's study files.

4.3.2 Premature Discontinuation from Investigational Product

A subject may be prematurely discontinued from IP dosing for any of the following reasons:

- Safety, including AEs or development of clinically significant laboratory abnormalities. The subject must be followed clinically until the event is resolved or deemed stable.
- Pregnancy.
- Subject wishes to withdraw consent for reasons other than an AE.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- Investigator discretion.
- Sponsor request.

Efforts will be made to follow all subjects who discontinue IP for any reason. Such follow up will include all relevant evaluations for safety including clinical assessments and collection of laboratory study results as set out in this protocol.

4.3.3 Premature Discontinuation from Study

A subject may be prematurely discontinued from the study for any of the following reasons:

- Subject wishes to withdraw consent for reasons other than an AE.
- Subject is lost to follow-up.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- Investigator discretion.
- Sponsor request.

4.3.4 Replacement of Subjects

Subjects who do not complete all study procedures, per protocol, through Day 29 (complete 14-day gluten challenge and second biopsy) may be replaced.

4.3.5 Study or Site Termination

Conditions may arise during the study that could prompt the study to be halted or the study site to be terminated. Conditions that may prompt such considerations include, but are not limited to, the following:

- The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of Sponsor to suspend, discontinue, or shorten the study.
- Study conduct at the study site may warrant termination under conditions that include the following:
    - Failure of Investigator(s) to enroll eligible subjects into the study.
    - Failure of Investigator(s) to comply with International Conference of Harmonisation-Good Clinical Practice (ICH-GCP) guidelines, or FDA guidelines and regulations.
    - Submission of false information from the research facility to the Sponsor, the Clinical Monitor, the FDA, or Institutional Review Board (IRB).
    - Insufficient adherence to protocol requirements.
    - A conflict of interest of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial.
    - Institution or IRB under investigation for cause by a regulatory agency.

5 INVESTIGATIONAL PRODUCT

5.1 TIMP-GLIA

TIMP-GLIA is comprised of gliadin extract within a negatively charged (-35mV to -50mV) polymer matrix of PLGA particles with an average size between 400 nm – 800 nm. There is approximately 10 μg of refined gliadin per mg of PLGA particles.

Prior to IV administration, TIMP-GLIA is reconstituted in sterile water for infusion and diluted in 0.9% Sodium Chloride Injection USP (normal saline).

5.1.1 Packaging and Labeling

TIMP-GLIA is manufactured, packaged, and labeled by the Sponsor's designee(s) in accordance with legal and regulatory requirements.

TIMP-GLIA is supplied as a lyophilized powder in a single-use, 20-mL glass vial containing approximately 1 mg refined gliadin and 100 mg of PLGA particles. Vials have rubber, siliconized, 20 mm single-vent gray stoppers and an aluminum, 20 mm, flip-off seal.

Each vial and carton will bear a label conforming to regulatory guidelines which identifies the contents and including required statutory phrases (e.g., "New Drug – Limited by Federal (US) law to investigational use."), and other required elements including but not limited to the sponsor name, lot number, expiry date or reevaluation date as applicable, and storage conditions.

5.1.2 Storage

TIMP-GLIA vials should be stored at 2°C to 8°C (36°F to 46°F) and protected from light in a secure, temperature-monitored, limited access location. A daily temperature log must be maintained and temperature excursions documented.

5.2 Placebo

The placebo for this study is 0.9% Sodium Chloride Injection USP (normal saline). Placebo should be stored at ambient room temperature in accordance with the product label.

5.3 Preparation of Investigational Product

Preparation of the TIMP-GLIA and placebo must be performed by a designated **unblinded site pharmacist** (or otherwise qualified personnel) in accordance with the Pharmacy Manual provided by the Sponsor.

Dose will be determined by subject weight on Day 1.

5.4 Blinding and Unblinding

Investigators, subjects, and all study staff with direct subject contact will be blinded to treatment assignment. A designated unblinded pharmacist (or otherwise qualified personnel) at each site

will prepare each dose. That individual should have no contact with the subjects and minimize contact with other site study personnel.

Because TIMP-GLIA is an opaque milky white suspension once reconstituted and diluted, and the placebo is a clear solution (normal saline), both the IV bag containing IP and the IV tubing will be covered at the time the IP leaves the pharmacy.

Unblinding of treatment assignment is discouraged. In the event of a medical emergency for which the identity of the treatment assignment is critical to the care of a subject, the Investigator should call the Medical Monitor to discuss. In the event that unblinding is deemed necessary, an unblinded statistician will provide the treatment assignment to the Medical Monitor who will provide the information to the Investigator. A decision to discontinue a subject from further IP administration is not a rationale to unblind the treatment assignment.

5.5 Administration of Investigational Product

TIMP-GLIA or placebo will be administered by unblinded, trained study personnel. TIMP-GLIA or placebo will be administered at the following escalating rates:

- 20 mL per hour for 15 minutes, then
- 40 mL per hour for the next 15 minutes, then
- 80 mL per hour for the duration of the infusion

The total infusion time will be approximately 2.5 hours. Additional instructions will be provided in the Pharmacy Manual provided by the Sponsor.

5.6 Management of Infusion Reactions

Subjects must be monitored closely for signs and symptoms of an IR. In the event of an IR, the infusion should be slowed, or stopped and restarted at a slower rate at the discretion of the Investigator. If a severe IR occurs (Grade 3 or 4 signs or symptoms), discontinue infusion and institute treatment as needed.

In addition, if a subject experiences an IR, the following procedures will be undertaken:

- A symptom driven physical examination to capture medically relevant details, including but not limited to, a thorough dermatologic examination; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.
- Vital signs (sitting or supine blood pressure, heart rate, and body temperature) will be captured at the time of the IR and at least every 15 minutes until the resolution or stabilization of the IR.
- Blood samples for serum cytokines, and C3a, C5a, SC5b-9 complement levels will be drawn at the time of the IR

The Investigator may administer any medically indicated pharmacologic agent or procedure intended to relieve symptoms (CAUTION: no other drugs may be mixed in the IP infusion bag).

Signs and symptoms of the IR and drugs given for treatment are to be recorded in the medical record and in the electronic case report form (eCRF).

Subjects experiencing a Grade 3 or 4 IR should be discontinued from further doses of IP. After the first experience of an IR that is ≤ Grade 2, the Investigator may elect to initiate the next infusion at a slower rate (start at 25% of rate in Section 5.5). All changes to infusion rate are to be recorded in the medical record and in the eCRF.

5.7 Gluten Challenge

Bob's Red Mill Vital Wheat Gluten (75-80% Protein) powder will be used for the gluten challenge. It will be supplied by the sponsor in individual foil packets, each containing approximately 6 g gluten (approximately 8.5 g of powder) per packet.

Subjects will consume 12 g of gluten for the first 3 days of the gluten challenge (Days 15-17); 2 packets per day. For the remainder of the gluten challenge (Days 18-28), subjects will consume 6 g of gluten per day; 1 packet. Packets of wheat gluten will be mixed into half to one cup of applesauce (subject choice) and consumed in one sitting.

Gluten packets should be stored in a refrigerated (2-8°C), dry location.

5.8 Investigational Product and Wheat Gluten Accountability, Dispensing, and Destruction

The Investigator (or designee) will maintain an accurate record of the receipt of the IP and wheat gluten as shipped by the Sponsor (or designee), including the date received. In addition, an accurate IP/wheat gluten disposition record will be kept, specifying the amount dispensed (vials and packets) to each subject and the date of dispensation.

At the completion of the study, all unused IP/wheat gluten supplies will be returned to the Sponsor (or designee) or disposed of by the site in accordance with the Sponsor's (or designee's) written instructions.

5.9 Prior and Concomitant Medications

Subjects may not receive a live vaccine within 28 days prior or a subunit vaccine within 14 days prior to Day 1 or planned vaccination prior to Day 35.

All prior and concomitant medications, including prescription and nonprescription medicines, will be reported in the eCRF beginning at Screening through the last study visit.

5.10 Other Study Restrictions

5.10.1 Food and Fluid Intake

With the exception of the gluten challenge (Days 15-28) subjects must adhere to a gluten free diet throughout the study. There are no other restrictions on food or fluid intake during the

study. Because of the large volume of whole blood drawn for isolation of PBMCs, subjects should be well-hydrated on the days of collection.

5.10.2 Subject Activity Restrictions

To reduce the occurrence of exercise induced elevated creatine kinase, subjects should be instructed to refrain from excessive physical activity (as defined by the Investigator) for 48 hours before each study visit.

5.10.3 Birth Control

Men and WOCBP must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, IUD, or use of spermicide combined with a barrier method (e.g., condom, diaphragm) for 28 days before and after receiving the IP.

5.11 Treatment Compliance

To ensure compliance with the dosing regimen, all doses will be administered at the investigational site by trained study personnel who have been delegated that responsibility by the Investigator.

Subjects will be observed consuming the wheat gluten on the first day of the challenge and report adherence on all subsequent days (Day 16 through Day 28). Additionally, subjects will have a urine gluten test on Days 15, 20, and 29.

6 STUDY PROCEDURES

Refer to Appendix 1 for the Schedule of Events.

6.1 Definitions and Descriptions of Assessments and Procedures

CD history – CD history should include date of diagnosis, date of biopsy proven diagnosis,, and date subject started GFD. A copy of the biopsy must be maintained in the subject's medical record.

CSI-M – modified celiac symptoms index (Appendix 3); to be used to assess symptoms before, during, and after the oral gluten challenge.

Complete physical exam – examination of the following systems: cardiovascular; dermatological; ear, nose, and throat; extremities; gastrointestinal; musculoskeletal; ophthalmological; neurological; respiratory.

Symptom-driven physical exam – brief, focused examination of the subject following medical history, including assessment for AEs.

Vital Signs - temperature, heart rate, blood pressure. Heart rate and blood pressure should be obtained after subject is resting for 5 minutes.

Small bowel biopsy – a small bowel biopsy will be performed by a qualified gastroenterologist at each site. All study gastroenterologists will be trained on the study-specific procedures for obtaining the biopsy, including the location and number of biopsies to be obtained, and procedures for storing and shipping of samples.

Serum chemistries* – glucose, calcium, albumin, total protein, carbon dioxide/bicarbonate (CO_2), chloride, potassium, sodium, total bilirubin (TBL), alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, creatine kinase.

* Fasting is required at screening only.

Hematology - hemoglobin, red blood cell count, white blood cell count and differential, platelet count.

Serum cytokines - IFN-gamma, IL1-beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-alpha

Whole blood – whole blood samples will be obtained for pharmacodynamic assays. Blood will be shipped to a central lab for processing into PBMCs.

Women of child bearing potential (WOCBP) - not surgically sterile or post-menopausal defined as age > 40 years without menses for ≥ 2 years.

AEs and SAEs – refer to Section 7.2.

6.2 Screening

Subjects will be screened to assess eligibility criteria within 45 days prior to Study Day 1 (first dose of IP). Prior to performing the assessments below, it is important to obtain the Subject ID from iMedNet eCRF.

The following assessments and procedures will be performed:

- Written informed consent
- Medical history, including celiac, dietary, and concomitant medications
- Demographics
- Complete physical exam, including vital signs, height and weight
- Electrocardiogram
- Laboratory Assessments, including:
    - Fasting serum chemistries
    - Hematology
    - Serum pregnancy test for WOCBP
    - HIV and hepatitis C virus serology; hepatitis B surface antigen
    - High definition allelic HLA testing
    - Celiac serology: IgA, tTG-IgA, DGP-IgG
- Small bowel biopsy - **the biopsy may be performed any time within the 45 days prior to Day 1/ randomization**
- Confirm eligibility

6.3 Randomization

Upon determination that a subject meets all eligibility criteria, the subject will be randomized to treatment assignment. Randomization should occur via eCRF on Study Day 1 just prior to IP administration.

6.4 On-Study Procedures

6.4.1 Study Days 1 (Dose 1) and 2

This visit will take approximately 5 hours, including observation for 2 hours after dosing. The following procedures will be performed prior to IP administration:

- Weight - to be used to calculate dose
- Symptom-driven physical exam
- Vital signs
- Laboratory Assessments, including:
    - Serum chemistries
    - Hematology

  - Urine pregnancy test for WOCBP
  - DGP-IgG
  - Serum cytokines
  - C1q binding level
  - C3a, C5a, SC5b-9 complement levels
  - Whole blood
  - Plasma for future research
- Assessment of concomitant medications
- Confirm eligibility
- IP administration

The following procedures will be performed at the times specified below, during and after IP administration:

- Vital signs at 15, 30, and 60 minutes after the start of infusion, end of infusion, and 2 hours after the end of the infusion
- C3a, C5a, SC5b-9 complement levels at 30 minutes after start of infusion and end of infusion
- Monitoring for AEs, including IRs

  In the event of an IR, blood samples for serum cytokines, and C3a, C5a, SC5b-9 complement levels will be drawn at the time of the IR.

The subject will return to the clinic 24 hours after the dose (Day 2) to have blood drawn for:

  - Serum cytokines
  - C3a, C5a, SC5b-9 complement levels
  - Plasma for future research

6.4.2 Study Days 8 (Dose 2) and 9

This visit will take approximately 5 hours, including observation for 2 hours after dosing. The following procedures will be performed prior to IP administration:

- Symptom-driven physical exam
- Vital signs
- Laboratory Assessments, including:
  - Serum chemistries
  - Hematology
  - Urine pregnancy test for WOCBP
  - DGP-IgG
  - Serum cytokines
  - C3a, C5a, SC5b-9 complement levels
  - PK sample
  - Plasma for future research
- Assessment of concomitant medications

- IP administration

The following procedures will be performed at the times specified below, during and after IP administration:

- Vital signs at 15, 30, and 60 minutes after the start of infusion, end of infusion, and 2 hours after the end of the infusion
- C3a, C5a, SC5b-9 complement levels at 30 minutes after start of infusion and end of infusion
- PK sample at end of infusion and 2 hours after the end of the infusion
- Monitoring for AEs, including IRs

  In the event of an IR, blood samples for serum cytokines, and C3a, C5a, SC5b-9 complement levels will be drawn at the time of the IR.

The subject will return to the clinic 24 hours after the dose (Day 2) to have blood drawn for:

- Serum cytokines
- C3a, C5a, SC5b-9 complement levels
- Plasma for future research

6.4.3 Study Day 15 – Beginning of Gluten Challenge

This visit will take approximately 2 hours, including observation for 1 hour after consuming the wheat gluten. The following procedures will be performed prior to consuming wheat gluten.

- Symptom-driven physical exam
- Vital signs
- Laboratory Assessments, including:
  - Serum chemistries
  - Hematology
  - DGP-IgG
  - Serum cytokines
  - C1q binding level
  - C3a, C5a, SC5b-9 complement levels
  - Whole blood
  - Urine gluten test
- Assessment of concomitant medications
- Subject to complete CSI-M questionnaire
- Assessment of AEs
- Consume first day of wheat gluten

Prior to discharge from the clinic, the site will dispense additional wheat gluten packets and the subject will be instructed on consuming wheat gluten on Study Days 16 through 28. Subjects should be instructed to call the site if they have any trouble with the gluten challenge.

6.4.4 Study Day 20

This visit will take approximately 1 hour and ***after*** the subject has consumed their daily wheat gluten. The following procedures will be performed:

- Assessment of adherence to gluten challenge
- Symptom-driven physical exam
- Vital signs
- Laboratory Assessments, including:
    - Serum chemistries
    - Hematology
    - C1q binding
    - DGP-IgG
    - Whole blood
    - Urine gluten test
- Assessment of concomitant medications
- Subject to complete CSI-M questionnaire
- Assessment of AEs

6.4.5 Study Day 29

This visit will take approximately 3 hours, including the biopsy. The following procedures will be performed:

- Small bowel biopsy - **the biopsy may be performed on Day 28 or Day 29**
- Assessment of adherence to gluten challenge
- Symptom-driven physical exam
- Vital signs
- Laboratory Assessments, including:
    - Serum chemistries
    - Hematology
    - C1q binding
    - DGP-IgG
    - Urine gluten test
- Assessment of concomitant medications
- Subject to complete CSI-M questionnaire
- Assessment of AEs

6.4.6 Study Day 35 (± 1 day) or Early Termination

This visit will take approximately 1 hour. The following procedures will be performed:

- Symptom-driven physical exam
- Vital signs
- Laboratory Assessments, including:
    - Serum chemistries
    - Hematology
    - Serum pregnancy test for WOCBP
    - C1q binding
    - DGP-IgG
- Assessment of concomitant medications
- Subject to complete CSI-M questionnaire
- Assessment of AEs

Subjects who discontinue the study after Day 17 (after 3-days of gluten challenge) will have the following additional procedures performed on Day 20:

- Whole blood
- Small bowel biopsy

6.5 Research Storage Samples

Approximately 3 mL of blood will be collected on Days 1, 2, 8, and 9, frozen and stored. In addition, 4 biopsy samples will be collected at the time of each biopsy. These stored samples may be used by the Sponsor or its research partners for celiac or celiac-related disease, for retesting of planned tests, for testing to learn more about how TIMP-GLIA works, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed on these samples without expressed consent of study subjects. At the conclusion of this study, these samples may be retained in storage by the Sponsor or its research partners for a period up to 15 years.

7 ADVERSE EVENTS

AEs will be reported in a manner consistent with the FDA Guidance for Industry and Investigators, "Safety Reporting Requirements for IND and BA/BE Studies," December 2012 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf).

7.1 Reporting Responsibilities

All AEs will be recorded in the eCRF, from Study Day 1 through Study Day 35. It is the responsibility of the Investigator or Subinvestigator(s) to perform periodic assessment of all AEs. Data describing AEs, including SAEs, will be entered in the subject's medical record and eCRF. SAEs will be reported to the Sponsor as described in Section 7.6.

Subjects who experience AEs, whether serious or not serious, should receive appropriate treatment and medical supervision as clinically indicated. All AEs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator.

7.2 Definitions

7.2.1 Adverse Event

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

7.2.2 Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening
- An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment,

they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room (ER) or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

If it is not certain that an event meets the above definitions of an SAE, contact the Medical Monitor to discuss.

7.2.3 Relatedness (Causality)

Causality assessment is required for AEs (and SAEs) that occur during clinical investigations. There is currently no standard international nomenclature to describe the degree of causality or relatedness of an AE with the IP. The following terms will be used during this study:

- **Likely** - Reasons to consider an AE likely related to treatment may include, but are not limited to the following:
  - Timing of the event relative to the administration of the IP
  - Location of the AE relative to the site of IP administration
  - Likelihood based on experience with similar products
  - There is a biologically plausible explanation based on the mechanism of action or mode of delivery of the treatment
  - The AE is repeated on subsequent treatments
  - No other explanation is likely
- **Unlikely** - An AE with no temporal association with the IP but rather related to other etiologies such as concomitant medications or conditions, or subject's known clinical state.

7.2.4 Severity

Severity will be reported in accordance with the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (Appendix 2, Toxicity Grading Scale).

If an appropriate listing is not present in this table for an AE, the AE will be graded as follows:

- **Grade 1 (Mild)** - No interference with daily activity
- **Grade 2 (Moderate)** - Some interference with daily activity but medical intervention not required (e.g., doctor visit and/or prescription medicine); over the counter medicine permitted
- **Grade 3 (Severe)** - Prevents daily activity and requires medical intervention (e.g., doctor visit and/or prescription medicine)
- **Grade 4 (Potentially Life-threatening)** - ER visit or hospitalization

7.3 Clinical Laboratory Abnormalities

Any laboratory abnormality deemed clinically significant by the Investigator should be reported as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is

changed sufficiently from Screening/Baseline so that in the judgment of the Investigator a change in management is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis (e.g., anemia) should be reported as the AE term. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

7.4 Physical Exam Abnormalities

Any physical exam abnormality deemed clinically significant by the Investigator at Day 1 should be reported as medical history. Any new physical exam abnormality deemed clinically significant by the Investigator during the study should be reported as an AE.

7.5 Pregnancy

No additional doses should be administered to a subject who becomes pregnant during the conduct of the trial. All remaining safety assessments should be performed. **All pregnancies that occur –including female partners of male subjects – during the study must be reported to the Sponsor and followed to conclusion. The outcome of each pregnancy must be reported.**

Pregnancy alone is not an AE, nor is an induced elective abortion to terminate a pregnancy without medical reason. However, an induced therapeutic abortion to terminate a pregnancy due to complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion is always considered an SAE.

7.6 Reporting of Serious Adverse Events

SAEs must be reported to the Sponsor or designee within 1 business day of becoming aware of the event by entering the data on the AE eCRF. If at the time the Investigator submits an initial SAE report the event has not resolved, the Investigator must provide a follow-up as soon as it resolves (or upon receipt of significant information if the event is still ongoing). All SAEs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Upon checking "serious" on the AE eCRF, a notification will be sent to the Medical Monitor and/or designee. Relevant eCRFs (including Medical History, Concomitant Medications, and Adverse Events) must also be completed to provide supporting documentation for the SAE. If there are additional documents that support the SAE (e.g., clinic or hospital records or procedure reports), they should be uploaded to the AE eCRF.

The Sponsor is responsible for notifying the relevant Regulatory Authorities of certain events. It is the Investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, IP-related events that occur during the clinical trial. Each site is responsible for notifying its IRB/EC of these additional SAEs.

7.7 Toxicity Management

All clinical and clinically significant laboratory AEs (i.e., toxicities) will be managed as outlined below.

- Clinical and clinically significant laboratory abnormalities will be graded according to the Toxicity Grading Scale in Appendix 2.
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before IP discontinuation, unless such a delay is not consistent with good medical practice.
- Any questions regarding toxicity management should be directed to the Medical Monitor.

7.7.1 Suspected Drug-Induced Liver Injury

- For any ALT or AST > 3x the upper limit of normal (ULN), the results will be confirmed by repeat testing within 3 calendar days of receipt of results and prior to further administration of IP. Testing for AP, TBL, direct bilirubin, and international normalized ratio (INR) will be obtained at the same time. The subject will also be assessed for signs and symptoms.
- If repeat testing shows that ALT or AST > 3x ULN, IP will be permanently discontinued and the subject will be monitored closely until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Subjects should be referred to a gastroenterologist for further hepatic investigations.
- Subjects will be permanently discontinued from further IP administration for any of the following laboratory abnormalities:
    - ALT or AST > 8x ULN
    - ALT or AST > 3x ULN and TBL 2x ULN or INR >1.5
    - ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

7.7.2 Other Grades 1 and 2 Laboratory Abnormality or Clinical Event

Administer IP at the discretion of the Investigator. If the event is an IR, follow instructions outlined in Section 5.6.

7.7.3 Other Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, IP may be administered if the event is considered to be **Unlikely** related to IP.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be **Likely** related to IP, IP will be discontinued/interrupted until the event is resolved. IP may be administered/restarted if the event is resolved within 24 hours and at the discretion of the Investigator. If the event is an IR, follow instructions outlined in Section 5.6.

7.7.4 Other Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered to be **Likely** related to IP, IP will be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the condition returns to baseline or is otherwise explained, whichever occurs first.
- IP may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 creatine kinase after strenuous exercise) or a clinical event considered unrelated to IP **after** discussion with the Medical Monitor.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size

For the primary efficacy endpoint, using a 2-sided 0.05 significance level, a statistical power of ~70%, and assuming an increase in mean IFN- ɣ SFUs in the placebo group of 75 (standard deviation [SD] 100) and in the TIMP-GLIA group of 5 (SD 10), 15 subjects per group will allow detection of a difference of 70 in mean reductions in SFUs between the TIMP-GLIA and placebo groups.

8.2 Analysis Conventions

Planned statistical analyses will be detailed in the Statistical Analysis Plan (SAP). This plan will be finalized prior to locking of the final data set and unblinding of results. The general principles are outlined below. Ad hoc exploratory analyses may be performed in addition to those specified, but no claims or conclusions will be drawn other than hypotheses to be tested in future clinical trials.

In general, descriptive statistics for continuous variables will consist of subject count, mean (or geometric mean), median, SD, and range; and descriptive statistics for categorical variables will consist of subject counts and percentages.

No imputation of values for missing data will be performed.

All pharmacodynamic, histology, PK, and safety data will be included in data listings and summaries.

8.3 Analysis Populations

The following populations will be used for analysis of the study data.

Safety population: All randomized subjects who receive at least 1 dose of IP. Subjects will be analyzed according to the treatment actually received.

PK population: All randomized subjects who receive 2 doses of IP. Subjects will be analyzed according to the treatment actually received.

Pharmacodynamic population: All randomized subjects who receive 2 doses of IP, complete at least the first 3 days of the gluten challenge (12 g per day for 3 days) and have pharmacodynamic results on Study Day 1, 15 and 20.

Histology population: All randomized subjects who receive 2 doses of IP, complete the gluten challenge per protocol and have both a baseline and Day 29 biopsy.

8.4 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and consist of (but not limited to) the following: age, height, weight, sex, ethnicity/race, and CD history.

Additionally, the number and percent of subjects with past and current medical disorders (i.e., Medical History) at Study Day 1 will be presented overall and by treatment group.

8.5 Pharmacodynamic Analyses

The mean changes from baseline in IFN-γ SFUs within and between treatment groups will be compared using a Wilcoxon Signed Rank Test and a Wilcoxon Rank Sum Test, respectively.

The proportion of subjects with a 2-fold increase from baseline (and an increase of at least 10) in IFN-γ SFUs in the placebo and TIMP-GLIA groups will be compared using a Fisher's Exact Test.

Descriptive statistics will be used to summarize the additional pharmacodynamic endpoints.

8.6 Histology Analyses

The mean changes from baseline in villus height, crypt depth, and their ratio (Vh:Cd) within and between treatment groups will be compared using a Wilcoxon Signed Rank Test and a Wilcoxon Rank Sum Test, respectively.

The proportion of subjects with a decrease of ≥ 0.4 in Vh:Cd in the placebo and TIMP-GLIA groups will be compared using a Fisher's Exact Test.

The mean changes from baseline in IELs within and between treatment groups will be compared using a Wilcoxon Signed Rank Test and a Wilcoxon Rank Sum Test, respectively.

8.7 Celiac Signs and Symptoms

Subject responses to the CSI-M will be summarized using descriptive statistics.

8.8 Pharmacokinetic Analyses

Individual subject TIMP-GLIA concentrations and derived PK parameters will be summarized using descriptive statistics, including coefficient of variation..

8.9 Safety Analyses

8.9.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). Frequency tables will be presented by treatment group for all AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT). Frequency tables will also be produced by treatment group for AEs leading to discontinuation from IP and study, by severity, and by causality. No formal statistical testing will be done.

Clinically significant physical exam and lab abnormalities will be reported as AEs, and summarized as described above.

8.9.2 Laboratory Evaluations and Vital Signs

Quantitative data (e.g. clinical lab results) will be summarized by mean, median, SD, and range. Laboratory abnormalities will be analyzed as safety outcomes by summarizing frequency, severity, and changes from baseline. Other analyses may include but are not limited to the following: examination of shift tables and pre-established severity grades.

8.9.3 Concomitant Medications

Concomitant medications will be coded using the most current World Health Organization (WHO) drug dictionary and summarized by drug class and medication term, with results presented by treatment group.

8.10 Interim Analysis

An interim analysis will be performed when Day 29 data are available for the 30 subjects. The analysis will involve looking at results for change from baseline in IFN-γ SFUs and change from baseline in Vh:Cd. The final sample size will be determined based on the operating characteristics for a decision criterion using a Bayesian approach applied to both of these endpoints. An additional 20 subjects (10 per arm) may be randomized based on the interim results. Details of this interim analysis will be provided in the SAP.

9 ETHICAL AND ADMINISTRATIVE RESPONSIBILITIES

9.1 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor, its authorized US representative and Investigator abide by good clinical practice (GCP) as described in the ICH guideline E6, and in US regulations described in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles that have their origins in the Declaration of Helsinki.

9.2 Institutional Review Board Approval

This protocol and the ICF and any subsequent modifications will be reviewed and approved by the relevant IRB responsible for oversight of the study. A letter from the IRB indicating approval of the study to be conducted by the Investigator will be provided to the Sponsor prior to initiation of any enrollment at that site. All reviews and approvals by the IRB will be in accordance with 21 CFR part 56.

9.3 Informed Consent

The ICF document must be signed and dated prior to the initiation of study-related tests, and prior to administration of IP. The original signed ICF for each participating subject shall be filed with records kept by the Investigators. A copy of the ICF must be provided to the subject. If applicable, the ICF will be provided in a certified translation of the local language.

9.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of the Sponsor, the IRB approving this research, and any applicable regulatory authorities will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subjects' identity will remain confidential.

9.5 Protocol Amendments

Any changes to the protocol will be made in writing by the Sponsor in the form of a protocol amendment. All protocol amendments will be sent to the Investigator, who is responsible for submitting the amendment to the IRB for approval.

9.6 Case Report Forms

An eCRF will be used to record subject data specified by this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be signed by the Investigator or a Sub-Investigator listed on the Form FDA 1572. It is the responsibility of the Investigator to ensure the eCRFs are completed and submitted to the Sponsor (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change and person making change).

9.7 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondences, computer printouts, laboratory data, and drug accountability records. All source documents produced in this study will be maintained by the Investigator(s) and made available for inspection by the Sponsor's representatives, the IRB, the FDA, or other regulatory authorities.

9.8 Retention of Records

US regulations (21 CFR part 312.62) require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs including medical records, eCRFs, ICFs, test results, and IP records be kept on file by the Investigator for 2 years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for 2 years after the investigation has been discontinued and the FDA has been notified. ICH guidelines indicate that documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. No study records should be destroyed without prior authorization from the Sponsor.

9.9 Study Monitoring

Site visits will be conducted by an authorized Sponsor representative (the monitor) to inspect study data, subjects' medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the respective US or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs.

The Investigator will permit representatives of the Sponsor, the IRB, the FDA, and/or respective health authorities to inspect facilities and records relevant to this study.

9.10 Protocol Deviations

Sites are responsible for abiding by their IRB rules and regulations for reporting protocol deviations. Additionally, the following important protocol deviations will be reported in the eCRF:

- Subject did not meet study eligibility criteria
- Subject did not receive the correct treatment assignment
- Subject received the wrong amount of a dose IP (i.e., ± 20% of assigned dose)
- Subject received a prohibited concomitant medication

A subject who has 1 of the above deviations will not receive further doses but will be followed for safety per protocol.

9.11 Financial Disclosure

Investigators participating in this study will provide accurate financial disclosure information to the Sponsor as required by 21 CFR Part 54. Investigators will update the financial information if any relevant changes occur during the study and for 1 year following completion of the study.

9.12 Publication and Disclosure Policy

Investigators and their staff shall hold confidential and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Sponsor's products or research programs that is provided to the Investigator. All such persons must be instructed not to further disseminate this information to others. Investigators shall not use the Confidential Information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by the Investigator shall not apply to: (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than disclosure by or through the Investigator; (c) information which, as evidenced by the Investigator's written records, was known by the Investigator prior to the Sponsor's disclosure; (d) information which is lawfully disclosed to the Investigator by a third party not under any obligation of confidence to the Sponsor; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to the Sponsor.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of the Sponsor. The Sponsor reserves the right of prior review of any publication or presentation of information related to the study. The Sponsor reserves the right of prior review of any publication or presentation of information related to this study. The Sponsor may use these data now or in the future for presentation or publication at the Sponsor's discretion or for submission to government regulatory agencies.

The Sponsor adheres to the general principles of publication of scientific data as articulated by the International Committee of Medical Journal Editors and acknowledges its responsibility to publish results of clinical trials. Persons that fulfill the criteria for authorship

(http://www.icmje.org/recommendations/) may be authors on publications based on their contributions to the design, conduct, results, and/or analysis of this clinical trial. Investigators will have access to the data from this clinical trial for the preparation of scientific presentations and publications subject to the requirements of confidentiality. The Sponsor reserves the right to review, within a reasonable time frame, results or analyses from data generated in this study that are intended for public presentation, including scientific meetings.

In signing this protocol, Investigator agrees to the release of the data from this study and acknowledges the above confidentiality and publication policy. The provisions of this Statement shall survive the completion of the study.

10 REFERENCES

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Appendix 1 Schedule of Events

	Screen	Dose 1		Dose 2		Gluten Challenge			EOS/ET
Study Day	**D -45 to -1**	**D1**	**D2**	**D8**	**D9**	**D15**	**D20**	**D29**	**D35 ± 1**
Informed consent	X								
Medical History, including celiac, dietary, and medication history	X								
Demographics	X								
Confirm eligibility criteria	X	X							
Complete physical examination	X								
Symptom-driven physical examination		X		X		X	X	X	X
Vital Signs [a]	X	X [b]		X [b]		X	X	X	X
Electrocardiogram	X								
Small bowel biopsy	X							X [c]	
Laboratory Tests									
Serum chemistries	X [d]	X		X		X	X	X	X
Hematology	X	X		X		X	X	X	X
High definition allelic HLA testing	X								
HCV and HIV serology; HBsAg	X								
IgA, tTG-IgA	X								
DGP-IgG	X	X		X		X	X	X	X
Pregnancy test (WOCBP only)	Serum	Urine		Urine					Serum
Urine gluten test						X	X	X	
Serum cytokines		X	X	X	X	X			
C1q binding level		X				X	X	X	X
C3a, C5a, SC5b-9 complement levels		X [e]	X	X [e]	X	X			
Whole blood for IFN- ɣ ELISpot [f]		X				X	X		
Whole blood for gliadin-specific T cell proliferation, cytokine secretion [f]		X				X	X		
CCI [redacted]									
Plasma for future research		X	X	X	X				
Blood for PK				X [g]					
Randomization		X							
Dosing		X		X					
Oral gluten challenge						D15-17: 12g; D18-28: 6g			
Concomitant medication assessment	X	X		X		X	X	X	X
CSI-M Questionnaire						X	X	X	X
AE assessment		X		X		X	X	X	X

a Vital signs include temperature, blood pressure, and heart rate; height and weight will be collected at the Screen Visit. Weight will be collected again on Day 1. Vital signs should be obtained after subject is resting for 5 minutes.

b On Days 1 and 8, vital signs will be obtained prior to dose and at 15, 30, and 60 minutes after the start of infusion, end of infusion, and 2 hours after the end of the infusion.

c Biopsy may be obtained on Day 28 or Day 29

d Fasting is required at screening only

e C3a, C5a, and SC5b-9 complement levels will be obtained pre-dose, 30 minutes after start of infusion, and end of infusion

f Pre-dose on Day 1, pre-gluten consumption on Day 15 and post-gluten consumption on Day 20

g Pre-dose, end of infusion, and 2 hours after the end of infusion

Appendix 2 Toxicity Grading Scale

Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Tables for Laboratory Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23-26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

Source: Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. Food and Drug Administration Center for Biologics Evaluation and Research. September 2007

Appendix 3 Celiac Symptom Index-Modified (CSI-M)

Question	1	2	3	4	5
1. Have you been bothered by pain or discomfort in the upper abdomen or the pit of the stomach during the past 7 days?	None of the time	A little of the time	Some of the time	Most of the time	All of the time
2. Have you been bothered by nausea during the past 7 days?	None of the time	A little of the time	Some of the time	Most of the time	All of the time
3. Have you been bothered by rumbling in your stomach during the past 7 days?	None of the time	A little of the time	Some of the time	Most of the time	All of the time
4. Has your stomach felt bloated during the past 7 days?	None of the time	A little of the time	Some of the time	Most of the time	All of the time
5. Have you been bothered by diarrhea during the past 7 days?	None of the time	A little of the time	Some of the time	Most of the time	All of the time
6. Have you been bothered by low energy level during the past 7 days?	None of the time	A little of the time	Some of the time	Most of the time	All of the time

Leffler DA, Dennis M, Edwards George J, Jamma S, Cook E, Schuppan D, Kelly CP. A Validated Disease Specific Symptom Index for Adults with Celiac Disease. Clinical Gastroenterology and Hepatology. 2009 Dec;7(12):1328-34, 1334.e1-3. Epub 2009 Aug 7.

Appendix 4 Amendment to the Protocol

Amendment 1, Protocol Version 2.0, XX December 2018

The overall purpose of the amendment is to:

- Update results from Phase 1 study, TGLIA-5.001
- Add an interim analysis after 30 subjects have completed Day 29 to determine whether additional subjects should be added
- Add collection of complement levels and serum cytokines at 24 hours following each infusion of Study Drug (Days 2 and 9)
- Add collection plasma for future research on Days 1, 2, 8, 9, 15; remove whole blood for future research on Days 1, 15, and 20
- Add collection of celiac signs and symptoms before, during, and after the oral gluten challenge
- Allow for inclusion of subjects with thyroid disease (Exclusion 6 – modified)
- Other minor changes

Effect on Informed Consent Form

- Add collection of complement levels and serum cytokines at 24 hours following each infusion of Study Drug (Days 2 and 9)
- Add collection plasma for future research on Days 1, 2, 8, 9, 15; remove whole blood for future research on Days 1, 15, and 20
- Add collection of celiac signs and symptoms before, during, and after the oral gluten challenge

Summary of Changes

Section	Change	Rationale
Synopsis and Section 2.1.2 Secondary Objectives	Modified: • To compare the proportion of subjects who have a ~~3~~**2**-fold increase (and an increase of at least 10) from baseline in IFN-γ SFUs following an oral gluten challenge in subjects treated with TIMP-GLIA or placebo.	Assay validated in prior Phase 0 study demonstrates a "responder" a the 2-fold increase level
Synopsis and Section 2.1.2 Secondary Objectives	Added: • **To compare celiac disease (CD) signs and symptoms before and during an oral gluten challenge in subjects**	Additional measure of efficacy

Section	Change	Rationale
	treated with TIMP-GLIA or placebo.	
Synopsis and Section 3.1 (Overall) Study Design, ¶2	Added: **Subjects will be asked to complete the Celiac Symptom Index-Modified (CSI-M) questionnaire on Days 15, 20, 29, and 35.**	Instrument to measure symptoms and timepoints for measurement
Synopsis and Section 3.1 (Overall) Study Design, ¶4	Added: Safety laboratory tests for complement levels (C3a, C5a, and SC5b-9), and serum cytokines will be performed on Days 1, **2**, 8, **9**, and 15. ~~Additional s~~Samples for C1q binding will be performed on Days 1, 15, 20, 29, and 35.	To obtain safety samples at 24 hours following each infusion of Study Drug Days 1 and 15 inadvertently left out of original protocol
Synopsis and Section 4.1 Inclusion Criteria	7. Intact spleen (**no history of splenectomy or splenic disorders**).	Clarification that assessment can be made by history
Synopsis and Section 4.2 Exclusion Criteria	Modified ~~6. Presence or history of celiac-associated thyroid disease or~~ Type 1 diabetes~~, regardless of current treatment~~. 16. Receipt of TIMP-GLIA in prior clinical trial. 21. Participation in an oral gluten challenge within ~~12~~ **6** months prior to Day 1.	Subjects with thyroid disease are allowed into the trial Subjects who have ever been exposed to TIMP-GLIA will be excluded A 6 month “washout” post-gluten challenge is a sufficiently long time period to allow for a return to baseline on a gluten free diet
Synopsis and Section 2.2.3 Criteria for Evaluation	Added: **CD Signs and Symptoms:** • **Responses to CSI-M (Appendix 3)**	Additional measure of efficacy
Synopsis – Statistical Methods, Sample Size	Added: **An interim analysis will be performed when Day 29 data are available for the 30 subjects. The final sample size will be determined based on the operating characteristics for a decision criterion using a Bayesian approach. An additional 20 subjects (10 per**	Interim analysis to determine the need for additional subjects

Section	Change	Rationale
	arm) may be randomized based on the interim results.	
Synopsis Statistical Methods, Analyses – Efficacy/ Pharmacodynamics, ¶2 and Section 8.5 Pharmacodynamic Analyses, ¶2	Modified: The proportion of subjects with a ~~3~~**2**-fold increase….	Consistency with endpoint definition
Synopsis Statistical Methods, Analyses – Efficacy/ Pharmacodynamics, ¶7	Added: **Subject responses to the CSI-M will be summarized using descriptive statistics.**	Provide analysis for endpoint
Synopsis Statistical Methods, Analyses – PK and Section 8.8 Pharmacokinetic Analyses	Deleted: ~~PK parameters will be calculated using noncompartmental methods.~~	Not enough timepoints for noncompartmental analysis.
Section 1.5 – Clinical Trials of TIMP-GLIA	Entire section updated to reflect current study status, and completion of Part B dosing.	Updated study status and findings
Section 5.3 Preparation of Investigational Product, ¶2	Added: **Dose will be determined by subject weight on Day 1.**	Clarification of dosing weight
Section 5.5 Administration of Investigational Product, ¶1	Modified: TIMP-GLIA or placebo will be administered by **un**blinded, trained study personnel.	Clarify that person administering Study Drug will be unblinded
Section 5.6 Management of Infusion Reactions, ¶2, bullet 3	Added: • **Blood samples for serum cytokines, and C3a, C5a, SC5b-9 complement levels will be drawn at the time of the IR**	Obtain information about cytokines and complement at the time of IR, in addition to protocol timepoints
Section 6.1 Definitions and Descriptions of Assessments and Procedures – CD History	Changed: CD history should include date of diagnosis, date of biopsy proven diagnosis, ~~signs and symptoms at the time of diagnosis and prior to starting a GFD~~, and date subject started GFD, ~~current signs and symptoms~~. A copy of the biopsy must be maintained in the subject's medical record.	Signs and symptoms will be collected using the CSI-M
Section 6.1 Definitions and Descriptions of Assessments and Procedures – CSI-M	Added: **CSI-M – modified celiac symptoms index (Appendix 3); to be used to assess symptoms before, during, and after the oral gluten challenge.**	Validated instrument to collect celiac symptoms

Section	Change	Rationale
Section 6.1 Definitions and Descriptions of Assessments and Procedures – Serum cytokine	Added: **IL-13**	Inadvertently left out of original protocol
Section 6.1 Definitions and Descriptions of Assessments and Procedures – Whole blood	Deleted: …whole blood samples will be obtained for pharmacodynamic assays ~~and future research~~.	Whole blood will not be collected for future research; replaced by plasma
Section 6.4.1 Study Day**s** 1 (Dose 1) **and 2**	Added the following procedure: Day 1 - **Weight - to be used to calculate dose** **- Plasma for future research** **-** C3a, C5a, SC5b-9 complement levels at ~~15~~ **30** minutes after start of infusion and end of infusion - Monitoring for AEs, including IRs **In the event of an IR, blood samples for serum cytokines, and C3a, C5a, SC5b-9 complement levels will be drawn at the time of the IR** **Day 2** **The subject will return to the clinic 24 hours after the dose (Day 2) to have blood drawn for:** **- Serum cytokines** **- C3a, C5a, SC5b-9 complement levels** **- Plasma for future research**	Specify that subject weight at Day 1 will be used to calculate dose Modifications and additions to timepoints for collection of complement and serum cytokines was made at the request of the DMC Plasma for future research will be used for additional/repeat safety assessments as needed
Section 6.4.2 Study Day**s** 8 (Dose 2) **and 9**	Added: Day 1 **- Plasma for future research-** C3a, C5a, SC5b-9 complement levels at ~~15~~ **30** minutes after start of infusion and end of infusion - Monitoring for AEs, including IRs **In the event of an IR, blood samples for serum cytokines, and C3a, C5a, SC5b-9 complement levels will be drawn at the time of the IR** **Day 2** **The subject will return to the clinic 24 hours after the dose**	Modifications and additions to timepoints for collection of complement and serum cytokines was made at the request of the DMC Plasma for future research will be used for additional/repeat safety assessments as needed

Section	Change	Rationale
	(Day 2) to have blood drawn for: **- Serum cytokines** **- C3a, C5a, SC5b-9 complement levels** **- Plasma for future research**	
Sections 6.4.3 Study Day 15 6.4.4 Study Day 20 6.4.5 Study Day 29, and 6.4.6 Study Day 35 (± 1 day) or Early Termination	Added: **• Subject to complete CSI-M questionnaire**	To assess celiac-specific symptoms before, during, and after the oral gluten challenge
Section 6.4.6 Study Day 35 **(± 1 day)** or Early Termination	Added: A window for Day 35	To provide flexibility for scheduling Day 35
Section 6.5 Research Storage Samples	Modified: Approximately ~~20~~ **3** mL of blood will be collected on Days 1,~~15~~ **2**, **8**, and ~~20~~ **9**, frozen and stored. In addition, ~~2~~ **4** biopsy samples will be collected at the time of each biopsy.	Plasma (and not whole blood) for future research will be used for additional/repeat safety assessments as needed 4 not 2 biopsy samples will be collected at each biopsy
Section 8.7 Celiac Signs and Symptoms	Added: **Subject responses to the CSI-M will be summarized using descriptive statistics.**	Describe analysis method for endpoint
Section 8.10 Interim Analysis	Added: **An interim analysis will be performed when Day 29 data are available for the 30 subjects. The analysis will involve looking at results for change from baseline in IFN-γ SFUs, and change from baseline in Vh:Cd. The final sample size will be determined based on the operating characteristics for a decision criterion using a Bayesian approach applied to both of these endpoints. An additional 20 subjects (10 per arm) may be randomized based on the interim results. Details of this interim analysis will be provided in the SAP.**	Interim analysis to determine the need for additional subjects
Section 10 References	Added: **Leffler DA, Dennis M, Edwards George J, Jamma S, Cook E, Schuppan D, Kelly CP. A**	Reference for CSI-M

Section	Change	Rationale
	Validated Disease Specific Symptom Index for Adults with Celiac Disease. Clinical Gastroenterology and Hepatology. 2009 Dec;7(12):1328-34, 1334.e1-3. Epub 2009 Aug 7.	
Appendix 1 Schedule of Events	Updated	To reflect changes to Section 6
Appendix 3 Celiac Symptom Index-Modified (CSI-M)	Added	Provide the instrument to be used