Title: A PHASE 1, FIRST-IN-HUMAN, 2-PART, MULTICENTER DOSE ESCALATION AND REPEAT DOSE STUDY OF THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF TIMP-GLIA IN SUBJECTS WITH CELIAC DISEASE

NCT Number: NCT03486990

Protocol Approve Date: 11 September 2018

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

- Named persons or organizations associated with the study.
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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

A PHASE 1, FIRST-IN-HUMAN, 2-PART, MULTICENTER DOSE ESCALATION AND REPEAT DOSE STUDY OF THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF TIMP-GLIA IN SUBJECTS WITH CELIAC DISEASE

Sponsor:	COUR Pharmaceutical Development Company, Inc. 2215 Sanders Road, Northbrook, IL 60062
Study Number:	TGLIA-5.001
IND Number:	17579
Compound:	TIMP-GLIA
Version:	10.0 Protocol Incorporating Amendment 9.0
Date:	11 September 2018

Previous Version(s): Version 1.0 / 18 Jul 2017
Version 2.0 / 28 Aug 2017
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Version 5.0 / 1 Dec 2017
Version 6.0 / 9 Feb 2018
Version 7.0 / 9 May 2018
Version 8.0 / 25 Jul 2018
Version 9.0 / 8 Aug 2018

Sponsor Contacts

Medical Monitor	Cour VP, Clinical Development and Regulatory Affairs	**24-Hour SAE Reporting**
PPD	PPD	PPD

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Study Title:	A Phase 1, First-in-Human, 2-Part, Multicenter Dose Escalation and Repeat Dose Study of the Safety, Tolerability and Pharmacokinetics of TIMP-GLIA in Subjects with Celiac Disease
Protocol Number:	TGLIA-5.001
Version/Protocol Date:	v 10.0, 11 Septmeber 2018 Protocol Incorporating Amendment 9.0

Protocol Accepted and Approved by:

PPD

Date
(dd mmm yyyy)

Date
(dd mmm yyyy)

II. INVESTIGATOR AGREEMENT

Study Title:	A Phase 1, First-in-Human, 2-Part, Multicenter Dose Escalation and Repeat Dose Study of the Safety, Tolerability and Pharmacokinetics of TIMP-GLIA in Subjects with Celiac Disease
Protocol Number	TGLIA-5.001
Version/Protocol Date:	v 10.0, 11 September 2018 Protocol Incorporating Amendment 9.0

I confirm that I have read all pages of this study. I understand the study protocol and agree to conduct the study according to the procedures therein and according to the International Conference on Harmonisation (ICH) and FDA Good Clinical Practices (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the GCP guidelines to enable them to work in accordance with the provisions of these documents.

Signature of Principal Investigator — Date (dd mmm yyyy)

Investigator Name (print or type)

Investigator's Title (print or type)

Location of Facility (City, State) (print or type)

III. PROTOCOL SYNOPSIS

Sponsor: COUR Pharmaceutical Development Company, Inc.	
Study Title: A Phase 1, First-in-Human, 2-Part, Multicenter Dose Escalation and Repeat Dose Study of the Safety, Tolerability and Pharmacokinetics of TIMP-GLIA in Subjects with Celiac Disease	
Test Product: TIMP-GLIA	
Name of Active Ingredients: poly(lactic-co-glycolic acid), gliadin	
Study Number: TIMP-GLIA -5.001	Study Phase: 1
Study Centers: Up to 6 centers	**Study Duration:** planned 3Q2017-3Q2018

Primary Objective:

The primary objective is to assess the safety and tolerability of TIMP-GLIA when administered intravenously (IV) as a single dose at ascending dose levels and as a repeat dose in subjects with celiac disease (CD).

Secondary Objectives:

The secondary objectives are:

- To characterize the pharmacokinetics (PK) of TIMP-GLIA based upon concentrations of TIMP-GLIA in plasma over time in subjects with CD .
- To establish a safe and tolerable dose that may be tested during a future Phase 2 Proof of Concept study in subjects with CD.

Exploratory Objective:

cci [redacted]

Study Design:

This study is a Phase 1, first-in-human (FIH), 2-part, multicenter study to assess the safety, tolerability and PK of TIMP-GLIA in subjects with CD. Part A includes an accelerated titration 2+2 and traditional 3 + 3 design with rapid dose escalationduring which successive cohorts of subjects will receive a single dose of TIMP-GLIA. Part B will follow as a repeat dose design using the dose level selected from Part A.

Consenting subjects will be screened within 28 days (Day -28 to -1) prior to admission to the clinical research unit on Day -1 for baseline assessments.

Part A

In Part A, eligible subjects (*at least 19 CD subjects*) will be enrolled into escalating dose cohorts (n = 2/cohort for 2 dose levels followed by n = 3/cohort for 5 dose levels). TIMP-GLIA will be administered as a single intravenous (IV) infusion on Day 1. A staggered dosing strategy will be used in Part A. One subject in a cohort will be dosed at a time and undergo medical observation in the clinic for at least 48 hours post-infusion.

At least 168 hours (7 days) will elapse prior to dosing the next subject. Adverse events (AEs), vital signs, pulse oximetry, and electrocardiograms (ECGs) and laboratory data (serum chemistry, coagulation, hematology and urinalysis, cytokines) from samples obtained through at least 24 hours post dose will be assessed before dosing the subsequent subject(s).

AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Published: May 28, 2009 [v4.03: June 14, 2010]) or most current version. If safety and tolerability are confirmed by the investigator, TIMP-GLIA will be administered to the next subject.

Dose Escalation, Part A

After all the subjects in a dose cohort complete study procedures through at least 168 hours (7 days) post dose the safety data will be reviewed by the Data Monitoring Committee (DMC). Dose escalation will proceed only if Study Stopping Criteria ("Study Stopping Rules") are not met. If dose-limiting toxicity (DLT) occurs in 1 of the subjects in a cohort in Part A, the DMC may decide to increase enrollment at the same dose level by 2 subjects (accelerated titration cohort) or by 3 subjects (standard 3+3). After a rate of DLTs has been identified for a specific dose in 3- or 6-subject cohorts, the DMC may recommend that up to a total of 12 subjects may be accrued at any dose level to better define the relationship between dose and emerging safety signals. It is also possible that the DMC could recommend an intermediate dose (lesser escalation) or reduced dose level (dose reduction) if warranted by the emerging safety data. Before continuing to Part B, available safety data for all subjects Part A through at least 168 hours (7 days) after dosing will be evaluated by the DMC.

Part B

Part B will evaluate 2 doses of TIMP-GLIA administered on Days 1 and 8. Two subjects will be enrolled into each of 3 cohorts at dose levels of 2, 4, and 8 mg/kg up to a maximum of 650 mg. Dose escalation will proceed only if Study Stopping Criteria ("Study Stopping Rules") are not met. If dose-limiting toxicity (DLT) occurs in 1 of the 2 subjects in a cohort, the DMC may decide to increase enrollment at the same dose level by 2 subjects. (2+2 design).

Clinic Residency and Visits

Subjects in both parts of the study will remain in the clinic from admission (Part A: Day -1; Part B: Day -1 and Day 7) through the final post-dose procedure at 48 hours (Part A: Day 3; Part B: Day 3 and Day 10) and will be thereafter discharged if safety parameters are acceptable to the investigator. Subjects will return to the clinical research unit for follow-up assessments and will be contacted by telephone as shown in the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2).

Duration of Study Period

Part A:

Total duration of the study investigational period is up to 91 days (screening up to 28 days + 1 treatment day + follow-up at Day 60 +/- 3 days). In addition, telephone follow-up by a health care practitioner is required after the Day 60 outpatient visit (i.e. Day 90, Day 120 and Day 180, all +/- 3 days).

Part B:

Total duration of the study investigational period is up to 91 days (screening up to 28 days + 2 treatment days, 7 days apart + follow-up at 60 +/- 3 days after last dose. In addition, telephone follow-up by a health care practitioner is required after the Day 60 outpatient visit (i.e. Day 90, Day 120 and Day 180, all +/- 3 days).

Dose Limiting Toxicity Definition:

- ACTCAE Version 4.0 Grade 3 or higher that is at least possibly related to TIMP-GLIA
- Suspected drug-induced liver injury (DILI) at least possibly related to TIMP-GLIA in any dosed subject indicated by
- ALT or AST > 3x upper limit of normal (ULN) and increase of total bilirubin > 2x ULN without evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome ("Hy's Law") or
- ALT or AST > 3x ULN and INR > 1.5x ULN or
- ALT or AST >8xULN or

- ALT or AST >5xULN for more than 2 weeks or
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Any other toxicity which in the opinion of the DMC would not allow continued dosing if this were a repeat dose study

Study Stopping Rules:

- First occurrence of a CTCAE Grade 4 or Grade 5 toxicity at least possibly related to TIMP-GLIA
- 2 or more of the same CTCAE Grade 3 toxicity considered to be at least possibly related to TIMP-GLIA (among total number of subjects dosed)
- 1 subject experiences a CTCAE Grade 3 toxicity considered to be at least possibly related to TIMP-GLIA in the same organ system as experienced by another subject at CTCAE Grade 2 or higher considered to be at least possibly related to TIMP-GLIA (at the same dose level).
- Any other toxicity which in the opinion of the DMC would have precluded administration of a second dose if this were a multi-dose study.

Safety Committee:

A Safety Committee was convened to monitor the safety of subjects up to the 2 mg/kg dose cohort. The Safety Committee included the: principal Investigators (PIs) or PI's delegate and a medical consultant with expertise in CD.

The role of the Safety Committee is described in prior versions of this protocol under which the 0.1 mg/kg, 0.5 mg/kg, and 1 mg/kg doses were administered.

Data Monitoring Committee:

An independent DMC will be commissioned for this study for dose levels ≥ 2 mg/kg. The DMC will be comprised of 3 physicians with expertise in immunology and/or vaccines clinical trials. A 4th physcician with expertise in CD will serve as an advisor to the DMC, but in a non-voting capacity.

The sponsor medical monitor will not be a member of the DMC. The sponsor medical monitor and other study team members will be available to answer questions of the DMC as necessary and during Open Sessions of the DMC. The medical monitor and other study team members will not participate in Close Sessions of the DMC. The DMC will perform ongoing safety surveillance. The medical monitor will be notified of any serious adverse event (SAE) and any CTCAE Grade 2 or greater adverse event within 24 hours of investigator's (or designee's) awareness of such an event. An ad hoc DMC meeting may convene to evaluate safety and tolerability data to determine if it remains acceptable to continue dosing (within cohorts at same dose level) or to dose escalate (between cohorts) or explore lower doses.

The DMC will evaluate the available safety data post-infusion, including but not limited to, AEs, vital signs, pulse oximetry, 12-lead ECGs and available laboratory results (hematology, chemistry, coagulation, and urinalysis, cytokines).

The following decisions may be made if stopping criteria ("Study Stopping Rules") are not met:

- Escalate the dose as planned
- Expand the dose cohort to 4 subjects (accelerated titration 2+2, Part A and Part B) or to 6 subjects (standard 3+3, Part A)

  After a rate of DLTs has been identified for a specific dose in 3- or 6-subject cohorts, the DMC may recommend that up to a total of 12 subjects may be accrued at any dose level to better define the relationship between dose and emerging the safety signals.
- Decrease the dose either to a previous lower dose or to an intermediate dose

- Escalate the dose to an intermediate level if warranted based on events in the previous cohort

The decision(s) of the DMC to continue dosing will be documented and provided to the investigators prior to dosing any new subjects.

Additionally, the DMC may meet ad hoc to determine if it remains acceptable to continue dosing.

Selection of Study Population:

At least 23 male and female subjects 18 to 75 years of age with historical evidence of biopsy-confirmed CD and who have negative celiac serology and quiescent CD symptomology and are otherwise healthy or with stable comorbidity at screening are planned to be enrolled.

Collectively, subjects will be enrolled at up to 6 clinical research sites in the United States.

Subjects who withdraw before receiving the first dose of study drug will be replaced. Subjects who withdraw after receiving study drug will be replaced at the sponsor's discretion.

After fully informing prospective subjects of the present study and obtaining their written informed consent, the investigator will perform screening tests. Based on the results of these screening tests, the investigator will identify "provisional subjects" (including reserve [alternate] subjects, if available). The provisional subjects will be individuals who meet the inclusion criteria without meeting any of the exclusion criteria. Ethical and scientific aspects, the study objectives, and individual health status up to the selection date will also be carefully considered during the selection process. The provisional subjects will be admitted to the study site on the day on Day -1, whereupon they will undergo the tests scheduled for that day and confirmatory assessment of study eligibility criteria. Those who are deemed eligible for enrollment will then be selected as enrolled subjects.

Eligibility Criteria:

Inclusion Criteria

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject provides written informed consent to participate as indicated by a signature on the informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is an adult man or women, 18 to 75 years of age, inclusive, at Screening Visit.
4. The subject has a body mass index (BMI) that is >16 kg/m^2 with a minimum body weight of 33 kg up to a maximum body weight of 129 kg, inclusive, at Screening Visit and if BMI <18 ("underweight") or >25 ("overweight" or "obese"), is otherwise healthy in the opinion of the investigator.
5. The subject has celiac disease characterized as follows:
   a. The subject has a history of biopsy-confirmed celiac disease (intestinal histology showing villous atrophy) according to expert guidelines current at the time of diagnosis; and
   b. The subject has no known gluten exposure for at least 10 days prior to the Screening Visit and is willing to maintain a gluten-free diet for the duration of the study; and
   c. The subject has a total immunoglobulin A (IgA) titer within normal limits or has partial IgA deficiency (~5% of celiac patients) defined by a reduced serum IgA level of 3 – 70 mg/dL at Screening
      AND
      The subject has negative or weak positive recombinant human transglutaminase (tTG)-specific IgA titer at Screening
      OR
      For a subject with selective IgA deficiency (~2% of celiac patients), deamidated gliadin peptide (DGP)-specific IgG titer is negative or weak positive at Screening.
6. If male subject, agrees to practice medically approved contraception that may include, but is not limited

to, abstinence, monogamous relationship with a female who is not of child-bearing potential, surgical sterilization procedure (vasectomy), and or condoms throughout the study.

If female subject, is not of child bearing potential (postmenopausal or premenopausal with surgical sterilization) or agrees to practice medically approved contraception that may include, but is not limited to, abstinence, monogamous relationship with a male who is post-surgical sterilization procedure (vasectomy), or agrees to use medically acceptable and highly effective birth control methods (e.g., an intrauterine device, a double-barrier method such as condom and spermicide or condom and diaphragm with spermicide, a contraceptive implant, injectable contraceptive, or oral contraceptive) throughout the study.

7. The subject is able and agrees to comply with study requirements.
8. The subject agrees not to participate in another interventional study while participating in the present study, defined as signing the informed consent form until completion of the last study visit.

Exclusion Criteria

1. The subject has a history of clinically confirmed immunoglobulin E (IgE)-mediated reaction and/or anaphylaxis to wheat (i.e., "wheat allergy"), barley or rye.
2. The subject has uncontrolled celiac disease and/or complications of celiac disease, or otherwise has experienced celiac symptomology within 10 days of screening, in the opinion of the investigator.
3. The subject has a history of, or has an active, significant, clinically relevant, comorbidity (including Type 1 and Type 2 diabetes mellitus and other autoimmune disorders, splenectomy) that, in the opinion of the investigator, would make the subject unsuitable for participation in the study and/or could adversely affect interpretation of the study results.
4. The subject has had significant changes to or anticipates changes to prescription or non-prescription medication used to manage an underlying comorbidity within 30 days prior to Day 1.
5. The subject is currently taking or received systemic biologics 6 months prior to Day 1.
6. The subject has a compromised immune system, e.g.:
   a. Known human immunodeficiency virus (HIV) infection or positive for HIV antibodies at Screening;
   b. Subject is or has been taking an immune suppressing medical treatment (e.g., azathioprine, methotrexate) during the 2 months prior to Day 1;
   c. Subject is receiving immunosuppressive doses of corticosteroids (more than 20 mg of prednisone given daily for 2 weeks or more within 2 months prior to Day 1 , any dose of corticosteroids within 30 days of Day 1, or high dose inhaled corticosteroids [>960 µg/day of beclomethasone dipropionate or equivalent]) within 30 days of Day 1.
7. The subject has a known history of hypersensitivity or allergies to TIMP-GLIA components or any other known severe hypersensitivity or allergic reaction (any reaction that resulted in hospitalization [initial or prolonged], congenital anomaly, or disability, or that required medical intervention to prevent permanent impairment or damage) to any other allergens (medications, food or environmental).
8. The subject has currently 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.
9. The subject has a history of any acute illness including, fever (>100.4°F or >38°C) within 14 days of Check-In Day-1.
10. The subject has an active malignancy, or history of malignancy or chemotherapy, within the past 5 years other than history of localized or surgical removal of focal basal cell skin cancer, cervical cancer in situ treated successfully in the past by local treatment (including but not limited to cryotherapy or

laser therapy) or by hysterectomy.

11. The subject has known liver disease or serology positive for hepatitis C infection; positive hepatitis B surface antigen (HBsAg) at Screening Visit.
12. The subject has a positive test result for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, methylenedioxymethamphetamine) or alcohol in urine – except when the positive result arises from treatment under supervision of a medical doctor - at Screening Visit or at Check-in.
13. The subject has a history of any drug or alcohol abuse in the past 5 years, or alcohol consumption greater than 21 units per week that, in the opinion of the investigator, would interfere with the subject's ability to comply with the study requirements. A unit of alcohol is equivalent to: 12 ounces of beer, 4 ounces of wine, or 1 ounce of spirits/hard liquor. Alcohol consumption will be prohibited 24 hours prior to entry into the clinical research unit until discharge.
14. The subject has the inability to undergo venipuncture or tolerate venous access as determined by the investigator or designee.
15. The subject has a history or presence of anorexia nervosa or other eating disorder.
16. If female, the subject is pregnant or lactating or intending to become pregnant before or during the study. The lack of pregnancy will be confirmed by serum assay for qualitative human chorionic gonadotropin (hCG) at Screening and a urine assay performed at Check-in. Women with postmenopausal status confirmed by screening follicle-stimulating hormone (FSH) result need not undergo subsequent urine pregnancy testing.
17. The subject has clinically significant laboratory results at Screening, as determined by the investigator, including, but not limited to the following:
    a. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) ≥ 1.5 times Upper Limit of Normal (ULN)
    b. Direct bilirubin outside the normal range
    c. Serum Creatinine > 1.2 mg/dL
    d. Hemoglobin < 10 g/dL
    e. Hematocrit < 30%
    f. Platelet count < 150,000 or > 400,000
    g. Serum Potassium, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), international normalized ratio (INR), or white blood cell count (WBC) outside the normal range (and judged clinically significant by the investigator)
18. The subject has clinically significant, abnormal electrocardiogram (EGC) at Screening, as determined by the investigator, including but not limited to:
    a. Mean QTcF interval >430 msec for males or >450 msec for females;
    b. ECG evidence of complete left bundle branch block (LBBB) or right bundle branch block (RBBB), or incomplete LBBB;
    c. Mean intraventricular conduction delay with QRS duration >120 msec;
    d. Pathological Q-waves, defined as Q-wave >40 msec or depth >0.4 to 0.5 mV;
    e. Evidence of ventricular preexcitation according to the investigator.
19. The subject has received any investigational drug within 30 days or 5 half-lives prior to first dosing/Day 1.
20. The subject was previously enrolled and dosed in a clinical trial with TIMP-GLIA.

21. The subject received a live or inactive vaccine within 28 days prior or a subunit vaccine within 14 days prior to first dosing/Day 1 or the subject has a planned vaccination during the study.
22. The subject has donated blood or plasma ≤ 56 days prior to Screening and plans to donate blood or plasma within 5 weeks of completing the study.
23. The subject has received blood products, monoclonal antibody, or other systemic protein therapy within 6 months prior to first dosing/Day 1. NOTE: oral protein supplements are permitted.
24. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
25. The subject is unsuitable for enrollment in the opinion of the investigator for any other reason not specified above.

Duration of Treatment:

Part A: Single IV infusion administered on Day 1

Part B: Two IV infusions, one administered on Day 1 and the other on Day 8

Test Product; Dose; and Mode of Administration:

Part A: TIMP-GLIA: 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg; 2 mg/kg; 4 mg/kg; and 8 mg/kg, administered by IV infusion.

Part B: TIMP-GLIA: 2, 4, and 8 mg/kg up to a maximum of 650 mg, administered by IV infusion.

Reference Therapy; Dose; and Mode of Administration: NA

Endpoints:[Note: Timed Procedures Are Relative To Infusion Start Time.]

Safety and Tolerability:

Safety will be characterized by incidence, severity, and reversibility of AEs, physical examination findings, 12-lead ECG results, arterial oxygen saturation levels by pulse oximetry, vital signs measurements, anti-gliadin antibody (i.e., anti-drug antibody as deamidated gliadin peptide (DGP)-specific IgG), immune complex detection by C1q binding and by C3a and SC5B-9 (Part B only); routine clinical laboratory test results (hematology, serum chemistry, coagulation, urinalysis) and other specialized laboratory test results (e.g., acute phase cytokines; additional vascular / thrombotic markers; mast cell activation via tryptase; additional complement markers, peripheral blood gliadin-specific T-cell proliferation and cytokine secretion). Post-dose assessment of peripheral blood T cell proliferation and cytokine secretion in response to ex vivo gliadin stimulation relative to baseline will be performed for the single dose groups ≥ 4 mg/kg in Part A and the for the repeat dose groups in Part B.

The analysis of samples drawn for cytokine testing (EGF, fractalkine, GM-CSF, GRO α, IFNα, IFN-γ, IL-1α, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, MIP1α, and MIP1β, TNF-α) should be performed as follows:

The IFN-γ, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, and TNF-α results through 24 hours post dose will be used for dose escalation decision (i.e., analyzed at the end of each dose cohort). This acute phase cytokine testing should be performed promptly and results are to be reported to the investigator as soon as possible in the event clinical symptoms occur. The scheduled predose and post dose samples for the other cytokines can be batched and analyzed at the end of the trial unless otherwise specified by the medical monitor, sponsor, or DMC or as necessary for compliance with the established sample stability.

Results of peripheral blood T-cell proliferation and cytokine secretion in response to ex vivo stimulation with gliadin will be reported at the end of the study or as otherwise specified by the sponsor, medical monitor, or DMC.

Tolerability will be characterized by extent of dose escalation attained without dose limiting toxicity.

Pharmacokinetics:

Individual subject TIMP-GLIA concentrations in plasma over time will be used to derive PK parameters by noncompartmental analysis. The primary PK parameters are maximal observed concentration (C_{max}), last measurable concentration (C_{last}), time of maximal observed concentration (T_{max}), time of last measurable concentration (T_{last}), and area under the curve from time zero and extrapolated to infinity (AUC_{inf}) and area under the concentration-time curve from time zero to time of the last measurable concentration (AUC_{last}). Other PK variables will be derived if feasible. The results of the PK analysis will be reported at the end of the study.

Statistical Methods:

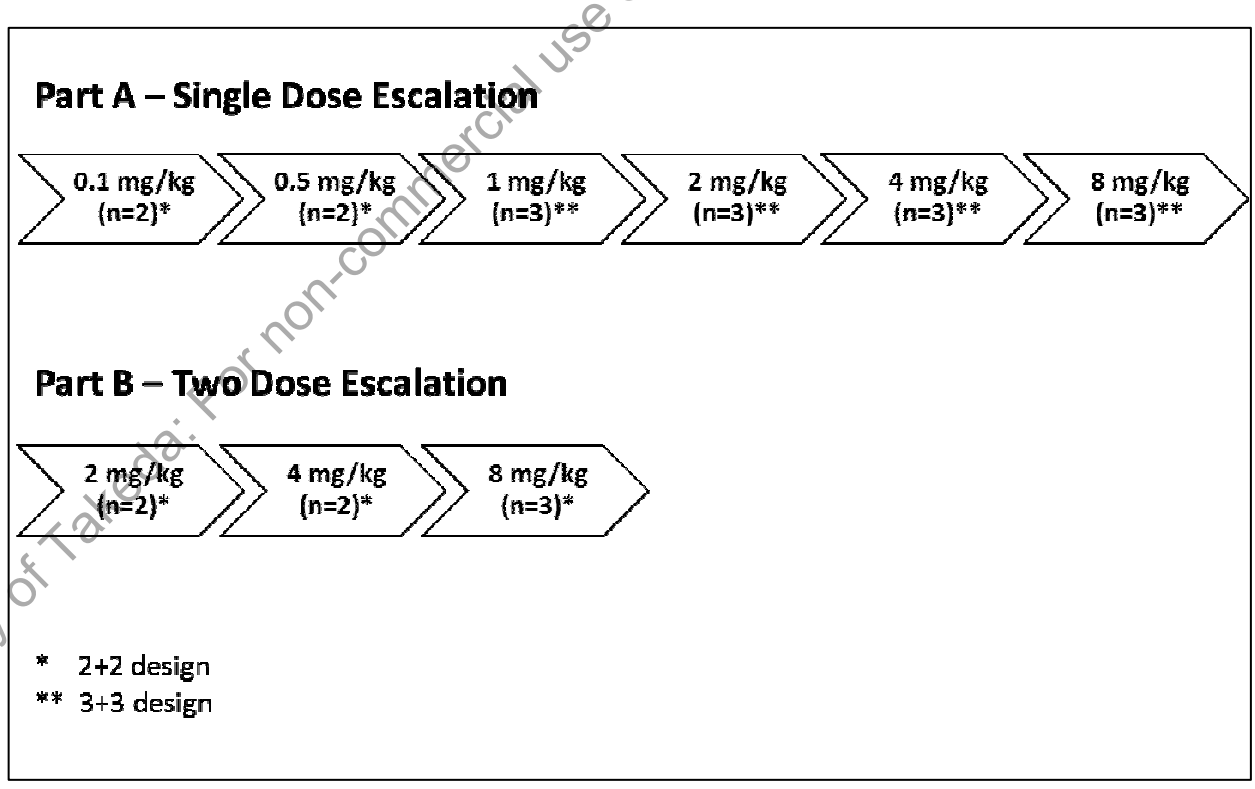
Safety

No formal statistical analyses will be conducted; all analyses will be descriptive. Quantitative data will be summarized by summary statistics and change from baseline.

Pharmacokinetics (PK):

Individual subject TIMP-GLIA concentrations and derived PK parameters which will be summarized using descriptive statistics (N, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum and geometric mean where applicable). The PK parameters will be calculated using noncompartmental methods.

Figure 1. Schematic of Planned Dosing in Subjects With Celiac Disease, Part A and Part B



IV. SCHEDULES OF ASSESSMENTS

Table 1. Schedule of Procedures, Part A

	Screening[†]		Investigational period*'***											Follow up period		
Study Day	-28 to -2	-1	1[†]	2	3	4	5	6	7±1 F/U	14±2 F/U	21±2 F/U	30 ±2 F/U	60±3 F/U	90±3 F/U	120±3 F/U	180±3 LFU
Clinic residency, outpatient visit or telephone contact visit	V	Adm			Dis	T	T	T	V	V	T	V	V	T	T	T
Informed Consent	X															
Inclusion and exclusion criteria	X	X[¶¶]														
Demographics, height, weight, BMI	X	X^														
Medical/medication/dietary history, baseline conditions	X	X				X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]
Physical examination	X[“]	X[”]			X[”]				X[”]	X[”]		X[”]	X[”]			
Vital signs[¶]	X	X	Predose, every 15 min during infusion, 2h, 4h, 8h, 12h, 24h		48h				X	X		X	X			
Pulse oximetry[‡]			Predose, 1h, 2h, 4h, 8h, 12h, 24h													
12-lead ECG[††]	3X	3X	Predose; 1h, 4h, 12h, 24h		48h				X[†††]	X[†††]		X[†††]	X[†††]			
Continuous real time ECG/telemetry[♥]			Predose-8h													
Contact designee re: enrollment, dose scheduling, screen failure	X	X	Predose									X	X			
Clinical chemistry tests[§]	X	X		24h	48h				X	X		X	X			
Pregnancy test (hCG) [§ **]	X	X							X	X		X	X			
Coagulation tests[§]	X	X		24h	48h				X	X		X	X			
Hematology[§]	X	X		24h	48h				X	X		X	X			
Hepatitis & HIV serology[§]	X															
Drugs of abuse & alcohol[§]	X	X														
Urinalysis + microscopic examination and UPCR[§]	X	X		24h	48h				X	X		X	X			
HLA-DQ2.5, HLA-DQ8.1[§§]			X													
Anti-drug antibody IgG[‡‡]	X		Predose		48h				X[Y]	X		X	X			
Immune Complex Detection by C1q Binding			Predose		48h				X[Y]	X		X	X			
IgA level, IgA-tTG, IgG-DGP serology [§, ‡‡‡]	X															
Cytokine (& chemokine) panel[§ ##]			Predose, 8h and prn[##]	24h					X	X						
Whole blood for PBMC isolation[§ #]			Predose and prn[#]						X							
Anaphylactic/anaphylactoid response testing[§ #]			Predose and prn[#]													
Pharmacokinetics TIMP-GLIA plasma			Predose (0hr), 30min, 35 min (or end of infusion), 1h, 4h, 12h, 24h		48h				144h							
Dose (intravenous infusion)*			X													
Adverse event recording^^	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication^^	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Adm: Clinic admission; Dis: Clinic discharge (Shading denotes clinic residency period); V: Outpatient visit; T: Telephone contact visit by a health care practitioner; BMI: body mass index; ECG: electrocardiogram; ESV: end-of-study visit; F/U: Follow-up; LFU: Late (last) follow-up; UPCR: urine protein to creatinine ratio; prn: pro re nata, as necessary; PBMC: Peripheral blood mononuclear cell

†Screening is the time from signing of informed consent up to but not including first administration of study drug, during which a subject is being evaluated for study eligibility.

*All post-dose times shown relative to infusion start time. Samples for PK are to be drawn from the opposite arm from which study drug is being infused. Subjects should remain supine during dosing.

¶¶Confirm eligibility. If the subject is found to be ineligible, record the reasons for screen failure in the source and the primary reason for screen failure in the applicable CRF.

^Weight only.

!!Inquiry regarding diet since prior visit (in-clinic or telephone)

«Full physical exam (PE) includes an assessment of general appearance, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest (lungs)/respiratory system, cardiovascular system, abdomen (liver, spleen), skin, extremities, musculoskeletal, neurological system (including mental status) and any other assessment not categorized but deemed necessary by the investigator.

»Abbreviated PE includes an assessment of general appearance, skin, chest (lungs)/respiratory system, cardiovascular system, abdomen (liver, spleen). Additional assessments/full PE may be conducted as clinically indicated at any time.

¶Vital signs except body temperature should be performed after the subject has been supine for at least 5 minutes. Vital signs include body temperature (oral and/or tympanic measurement), blood pressure (SBP and DBP), pulse (beats per minute) and respiratory rate (breaths per minute).

‡Pulse oximetry will be monitored from approximately 1 hour prior to the start of study drug infusion (0 hour) through 4 hours post dose and values also recorded at times indicated.

§See in-text Table 9, Clinical Laboratory Tests, for list of specific tests.

**Women with postmenopausal status confirmed by screening follicle-stimulating hormone (FSH) result need not undergo subsequent urine pregnancy testing.

#Symptoms of anaphylactoid/anaphylactic response or infusion-related reaction (IRR) (e.g., fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea) will be followed up with additional laboratory testing for vascular / thrombotic markers (e.g., von Willebrand Factor [vWF], intercellular adhesion molecule [ICAM-1]), mast cell activation (tryptase), complement markers (C3a, C5a, CH50, C5-9) and for T cell proliferation and cytokine secretion in response to ex vivo gliadin stimulation for ≥ 4 mg/kg dose cohorts. Samples are to be drawn predose Day 1, as needed to follow up signs/symptoms of anaphylactoid/anaphylactic response or IRR, and on Days 7 and 14.

##Samples are to be drawn predose and post dose as shown but additional samples for cytokine (& chemokine) panel are to be drawn post dose if clinically indicated (by appearance of systemic symptoms of anaphylaxis/anaphylactoid reaction or IRR such as fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea).

††ECGs in triplicate ("3X"), 1 minute apart, within 5 minutes (predrug baseline). Scheduled ECGs at other timepoints will be performed as a single measurement ("X"). All ECGs should be performed after the subject has been supine for at least 5 minutes.

†††Follow–up visit ECG only necessary if prior ECG was abnormal, clinically significant.

♥Continuous, real-time cardiac monitoring (telemetry) will be monitored starting approximately 1 hour prior to the start of study drug infusion (0 hour) through 8 hours post dose.

§§Perform phenotyping for HLA-DQ2.5 (HLA-DQA1*0501 / B1*0201) and HLA-DQ8.1 (DQA1*0301/B1*0302) if unknown OR if historical documentation not available. Sample may be taken any time on Day 1 from an enrolled subject.

‡‡Anti-gliadin antibody test which serves as an anti-TIMP-GLIA antibody test (anti-drug antibody test) will be deamidated gliadin peptide (DGP)-specific IgG antibody (IgG-DGP).

YSample should correspond to the 144 hour PK sample.

‡‡‡Additional tissue transglutaminase (tTG)-specific IgA antibody or deamidated gliadin peptide (DGP)-specific IgG antibody (IgA-tTG or IgG-DGP) serology is to be performed post dose upon appearance of celiac disease-related symptoms as determined by the investigator.

^^Adverse events (AEs) and concomitant medication will be collected from the time of signing of the informed consent through the final follow up. Treatment-emergent AEs will be differentiated at time of first dosing. Data collected during scheduled in-clinic or telephone visits and any spontaneously reported information through the AE reporting period are to be documented in the subject's record.

***The procedures as listed under the Study Day 14 visit should be performed as the final study procedures in the event a subject discontinues the study prematurely during the investigational period. If the subject discontinues on or before Day 7, a PK sample should also be collected, if possible, provided no other PK samples were already collected on the day of discontinuation.

Table 2. Schedule of Procedures, Part B

	Screening[†]		Investigational period*'***														Follow up period		
Study Day	-28 to -2	-1	1[†]	2	3	4-6	7	8	9	10	11-13	14±1 F/U	21±2 F/U	28±2 F/U	38±2 F/U	60±3 FU	90±3 FU	120±3 FU	180±3 L/FU
Clinic residency, outpatient visit or telephone contact visit	V	Adm			D1[§]	T	Adm			D1[§]	T	V	V	T	V	V	T	T	T
Informed Consent	X																		
Inclusion and exclusion criteria	X	X[¶¶]																	
Demographics, height, weight, BMI	X	X^					X^												
Medical/medication/dietary history, baseline conditions	X	X				X[‼]	X[‼]				X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]	X[‼]
Physical examination	X[“]	X[”]			X[”]		X[”]			X[”]		X[”]			X[”]	X[”]			
Vital signs[¶]	X	X	Predose, every 15 min during infusion, 2h, 4h, 8h, 12h, 24h		48h		X	Predose, every 15 min during infusion, 2h, 4h, 8h, 12h, 24h		48h		X			X	X			
Pulse oximetry[‡]			Predose, 1h, 2h, 4h, 8h, 12h, 24h					Predose, 1h, 2h, 4h, 8h, 12h, 24h											
12-lead ECG[††]	3X	3X	Predose; 1h, 4h, 12h, 24h		48h		X	Predose; 1h, 4h, 12h, 24h		48h		X[†††]			X[†††]	X[†††]			
Continuous real time ECG/telemetry[♥]			Predose-8h					Predose-8h											
Contact designee re: enrollment, dose scheduling, screen failure	X	X	Predose												X	X			
Clinical chemistry tests[§]	X	X		24h	48h		X		24h	48h		X			X	X			
Pregnancy test (hCG) [§ **]	X	X					X					X			X	X			
Coagulation tests[§]	X	X		24h	48h		X		24h	48h		X			X	X			
Hematology[§]	X	X		24h	48h		X		24h	48h		X			X	X			
Hepatitis & HIV serology[§]	X																		
Drugs of abuse & alcohol[§]	X	X					X												
Urinalysis + microscopic examination and UPCR[§]	X	X		24h	48h		X		24h	48h		X			X	X			
HLA-DQ2.5, HLA-DQ8.1[§§]			X																
Anti-drug antibody IgG[‡‡]	X		Predose		48h		X[Y]	Predose		48h		X[Y]			X	X			
Immune Complex Detection by C1q Binding			Predose		48h		X[Y]	Predose		48h		X[Y]			X	X			
IgA level, IgA-tTG, IgG- DGP serology[‡‡‡]	X																		
Cytokine (& chemokine) panel[§ ##]			Predose, 8h and prn[##]	24h				Predose, 8h and prn[##]	24h			X	X						
Whole blood for PBMC isolation[§ #]			Predose and prn[#]					Predose and prn[#]				X[Y]							
Anaphylactic/anaphylactoid response testing[§ #]			Predose and prn[#]					Predose and prn[#]											
C3a, C5a, and SC5B-9 complement levels			15 min, 30 min	24h				15 min, 30 min	24h										
Pharmacokinetics TIMP-GLIA in plasma			Predose (0hr), 30min, , 1h, end of infusion, 4h, 12h, 24h		48h		144h	Predose (0hr), 30min, , 1h, end of infusion, 4h, 12h, 24h		48h		144h							
Dose (intravenous infusion)*			X					X											
Adverse event recording^^	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication^^	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Adm: Clinic admission; Dis: Clinic discharge (Shading denotes clinic residency period); V: Outpatient visit; T: Telephone contact visit by a health care practitioner; BMI: body mass index; ECG: electrocardiogram; ESV: end-of-study visit; F/U: Follow-up; LFU: Late (last) follow-up; UPCR: urine protein to creatinine ratio; prn: pro re nata, as necessary; PBMC: peripheral blood mononuclear cell

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##Samples are to be drawn predose and post dose as shown but additional samples for cytokine (& chemokine) panel are to be drawn post dose if clinically indicated (prn) (by appearance of systemic symptoms of anaphylaxis or anaphylactoid reaction or infusion-related reaction such as fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea).

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†††Follow–up visit ECG only necessary if prior ECG was abnormal, clinically significant.

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Y Sample should correspond to 144 hour PK.

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V. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APCs	Antigen presenting cells
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	Aminotransferase
AUC	Area under the concentration-time curve
AUC_t	Area under the curve from time zero (time of dosing) to time t, where a relevant t will be determined based upon the observed data
AUC_τ	Area under the curve over the dosing interval, τ
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to time infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last measurable concentration (C_{last})
BSA	Body surface area
BMI	Body mass index
C3a, C5a	Complement proteins
CD	Celiac disease
CD3	Cluster of Differentiation 3
CFR	Code of Federal Regulations
CH50	Total complement activity test
C_{last}	Concentration of study drug corresponding to the time of the last measurable concentration
CL	Total body clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
(e)CRF	(Electronic) Case report form
CRO	Contract research organization
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte antigen
D-dimer	Fragment D-dimer, Fibrin degradation fragment
DGP	Deamidated gliadin peptide
DILI	Drug-induced liver toxicity
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee

DTH	Delayed type hypersensitivity
ECG	Electrocardiogram
EGF	Epidermal growth factor
ESV	End-of-study visit
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFD	Gluten-free diet
GGT	γ-Glutamyl transferase
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage colony stimulating factor (also known as colony stimulating factor 2, CSF2)
GMP	Good Manufacturing Practice
GRO α	Growth regulated alpha protein (also known as chemokine (C-X-C motif) ligand 1 [CXCL1])
HAV	Hepatitis A virus
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HED	Human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICAM-1	Intercellular adhesion molecule 1 (also known as cluster of differentiation 54 [CD54])
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN-α	Interferon alpha
IFN-γ	Interferon gamma
IgA, IgE, IgG	Immune globulin A/E/G antibodies
IL-10	Interleukin 10
IL-1α	Interleukin 1 alpha (also known as hematopoietin 1)
IL-1β	Interleukin 1 beta, also known as leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-6	Interleukin 6

IL-8	Interleukin 8
IL-12	Interleukin 12
IL-13	Interleukin 13
IL-15	Interleukin 15
IL-17	Interleukin 17
IND	Investigational New Drug
INR	International normalized ratio
IP-10	IFN-γ-induced protein (also known as C-X-C motif chemokine [CXCL-10] or small-inducible cytokine B10)
IRB/IEC	Institutional review board/Independent ethics committee
IRR	Infusion-related reaction
IV	Intravenous(ly)
LA-CRF	Liver abnormality case report form
LDH	Lactate dehydrogenase
LFT	Liver function test(s) (e.g. bilirubin, INR)
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LT	Liver test(s) (e.g., enzymes)
MARCO	MAcrophage Receptor with COllagenous
MedDRA	Medical Dictionary for Regulatory Activities
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MHC	Major histocompatibility complex
MIP-1α	Macrophage inflammatory protein (also known as chemokine (C-C motif) ligand 3, [CCL3])
MIP-1β	Macrophage inflammatory protein (also known as chemokine (C-C motif) ligand 4, [CCL4])
MRSD	Maximum recommended starting dose
MTD	Maximum tolerable dose
NCI	National Cancer Institute
NCL	Nanotechnology Characterization Laboratory
NCS	Not clinically significant
NOAEL	No observed adverse effect level
PAD	Pharmacological active dose
PBMC	Peripheral blood mononuclear cell
PDAS	Pharmacodynamic analysis set
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PLGA	Poly(lactic-co-glycolic acid)

POC	Proof-of-concept
PT	Prothrombin time
PTT	Partial thromboplastin time
R_{acc}	Accumulation index
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC5B-9	Complex of complement proteins, C5b-6-7-9 (also known as C5-9 complex)
SD	Standard deviation
SOP	Standard operating procedure
SWI	Sterile water for injection
$t_{½}$	Terminal elimination half-life
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIMP-GLIA	Tolerogenic Immune Modifying Particles-Gliadin
TLFs	Tables, listings and figures
T_{max}	Time of the maximum observed concentration
TNF-α	Tumor necrosis factor alpha
TT	Thrombin time
tTG	Tissue transglutaminase antibodies
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
WBC	White blood cell
WHO	World Health Organization
WHO-Drug	World Health Organization's Drug Dictionary
V_d	Volume of distribution
λz	Terminal rate constant

Definition of Key Terms

Terms	Definition
Baseline	Observed values/findings which are the starting point for comparison.
Clinical study entry	To register or enter into a clinical study, i.e., upon signing of informed consent form. Once a subject has provided written informed consent the protocol applies to the subject.
Clinical study period	Period of time from the first subject signing informed consent to the last subject's last visit.
Enrollment	A subject is enrolled in a clinical study when he/she has signed the informed consent form and all screening procedures have been successfully completed, the subject is confirmed eligible (inclusion/exclusion criteria) and starts the interventional phase of the clinical study. Subjects who fail to pass screening are not enrolled.
Dose limiting toxicity	Dose-limiting toxicity is defined to be a toxicity that prevents further administration of the agent at that dose level.
Intervention	The study drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a clinical study (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time during which the major protocol objectives are observed, and the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning clinical study subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	1) Process for retrieving candidates for the clinical study. 2) Process of active consideration of potential subjects for enrollment in a clinical study during the screening period.
Screening failure	Potential subject who did not meet 1 or more eligibility criteria required for participation in a clinical study or any subject who did pass screening but was not randomized/allocated to or who did not receive treatment.
Screening period	Period of time before a subject's entering the investigational period; i.e., from the time of a subject signing informed consent until just before the test drug or comparative drug (sometimes without randomization) is first given to a subject.
Source data	All information in original records and certified copies of the original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the clinical study. Source data exist in source documents (original records or certified copies) or in an electronic data capture system.
Source documents	Original documents, data and records including source data.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

1.1 Celiac Disease Overview

Celiac disease (CD) is a common immunological disorder with an estimated prevalence of 0.3 to 2.4% among people of European ancestry (Fasano 2012). It develops in genetically predisposed subjects as a consequence of an abnormal 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)-DQ/8 or HLA-DQ2 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; Leffler 2017; Mazzarela 2008; Tack 2010)

The enteropathy resulting from the T cell activation produces the chronic diarrhea, abdominal distension/pain, constipation, and other gastrointestinal symptoms, increased intestinal permeability, malabsorption, and occult gastrointestinal bleeding commonly observed in CD. Other manifestations might include weight loss, chronic fatigue, osteoporosis, refractory iron deficiency, anemia, infertility, growth failure in children, arthritis, peripheral neuropathy, dermatitis herpetiformis, gluten ataxia, and malignancy (Farrell 2002; Fasano 2012; Fasano 2001; Green 2007; Leffler 2017). In rare cases CD patients, primarily children, experience a life-threatening metabolic emergency termed celiac crisis, characterized by hypokalemia and acidosis secondary to profuse diarrhea (Baranwal 2003, Farrell 2002; Fasano 2012).

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 disease such as cancer. Numerous therapies have been designed to induce immune tolerance in autoimmune diseases. However, these treatments have yielded only marginal efficacy in clinical trials (Kaukinen 2014).

1.2 Investigational Product: 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 may also be thought of as a noninfectious disease therapeutic vaccine or "inverse vaccine" (Steinman 2010).

TIMP-GLIA is comprised of gliadin extract drug substance within a negatively charged polymer matrix of PLGA (Poly(DL-lactide-coglycolide)) particles. TIMP deliver the gliadin antigen via natural phagocytosis of the PLGA particles, a noninflammatory process. This phagocytosis of the particles leads to antigen presentation of the gliadin by antigen presenting cells (APCs) primarily in the spleen and liver. The gliadin specific T cells become anergic, or are deleted, or switch to T regulatory cells, thereby tolerizing the immune system to the gliadin antigen, and eliminating the deletirious immune cascade typically initated by the gliadin specific T cells in response to gliadin. TIMP-GLIA is designed and directed to specifically address and abrogate the T cell response that drives CD. (Getts 2015)

1.3 Nonclinical Studies

The safety and potential efficacy of TIMP-GLIA has been evaluated and supported in a robust set of nonclinical studies, including: a panel of in vitro nanoparticle characterization studies as described by the National Cancer Institute (NCI) Nanotechnology Characterization Laboratory (NCL) for assessing the potential toxicity and immune effects of nanoparticle therapeutics; in vivo pharmacology studies in mice; in vivo toxicology studies in rats; and an ex vivo study of T cell proliferation/mitogenicity and cytokine secretion in human peripheral blood mononuclear cells (PBMCs) (Phase 0) from both celiac and non-celiac subjects. The distribution, metabolism, and excretion of nanoparticles is also well-published. For detailed information refer to the Investigator's Brochure for TIMP-GLIA (Edition 1, 2017 or subsequent editions as they become available).

1.3.1 Pharmacology/Mechanism of Action

Splenic and liver APC populations express numerous scavenger receptors which during homeostasis play an important role in the recognition and recycling of dying leukocytes, red blood cells, and other debris on a daily basis. Targeting of and tolerogenic stimulation of APCs is crucial for immune tolerance induction. Importantly, these activities occur without triggering inflammation or breaking peripheral immune tolerance. TIMP have been designed to take advantage of this targeting pathway. All previously attempted immune tolerance strategies either using monoclonal antibodies (i.e., anti-CD3, cytotoxic T-lymphocyte antigen 4 [CTLA-4]) or small molecules (rapamycin) have not exploited this pathway. Specifically, the TIMP mechanism of action depends upon uptake of particles by APCs, particularly splenic marginal zone macrophages expressing scavenger receptors, such as the MAcrophage Receptor with COllagenous structure (MARCO), in a fashion similar to the clearance of apoptotic debris. Studies using particles or apoptotic cells have shown that treatment induced production of the regulatory cytokines interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) in the spleen, as well as upregulation of inhibitory ligands on macrophages, such as programmed death-1 (PD-1).

Downstream events include the induction of T cell anergy and the activation of regulatory T cells. The overall result is abrogation of pro-inflammatory T cell activity, reduction of leukocyte accumulation in tissues, and importantly, disappearance of signs of disease. (Getts 2015).

1.3.2 Pharmacology

1.3.2.1 In vitro Pharmacology

The in vitro nanoparticle studies focused on hematology [blood contact] (hemolytic potential, platelet aggregation potential, complement activation potential, effects on coagulation), immunology (effect on granulocyte and macrophage colony formation, macrophage nitric oxide production, chemotaxis, phagocytosis, maturation of dendritic cells) and cytotoxicity (caspase 3 and caspase 3/7 activation, MTT and LDH release) and oxidative stress (levels of glutathione, lipid peroxidation, reactive oxygen species) of liver cell preparations. Test concentrations of TIMP-GLIA in mg/mL were translated to "human equivalent doses" (HEDs) for these studies assuming an estimated human blood volume of 5.6 L for an average 70 kg human.

Collectively, key findings in the in vitro studies demonstrated that:

- No effects of TIMP-GLIA indicative of toxicity on hemolytic potential, platelet aggregation, complement activation and prothrombin time (PT, extrinsic pathway) were observed at HEDs as high as 162 mg/kg (applied concentration 2 mg/mL). Prolonged activated partial thromboplastin time (aPTT, intrinsic pathway) and thrombin time (TT, common pathway) were observed at HED 162 mg/kg, and for TT at HED 16 mg/kg (applied concentration 0.2 mg/kg); however, the data generated were considered to be inconclusive due to potential assay interference from the nanoparticles at higher concentrations.
- TIMP-GLIA was not associated with overt macrophage activation, increased dendritic cell (DC) maturation, and was not a chemoattractant at HEDs up to 162 mg/kg. A decrease in expression of DC surface antigens was observed with the highest HED (162 mg/kg; applied concentration 2 mg/mL) ascribed to nanoparticle interference with the assay.
- TIMP-GLIA was not associated with any hepatocyte toxicity at HEDs as high as 200 mg/kg. A finding of increased caspase 3/7 activity at HED 400 mg/kg (5 mg/mL applied concentration) that was attributed to assay interference by the nanoparticle. Similarly, TIMP-GLIA was not associated with oxidative stress (increased fluorescence response from oxidation of dichlorofluorescein diacetate [DCFH-DA]) at any concentration tested up to HED 400 mg/kg (applied concentration of 5 mg/mL). Decreased DCFH-DA fluorescence response was observed for HEDs of 24.8, 100, 200, and 400 mg/kg (applied concentrations of 0.31, 1.25, 2.5, 5 mg/mL, respectively) for which particle interference with the assay was suspected.

1.3.2.2 In vivo Pharmacology (Mouse)

Primary pharmacology of TIMP GLIA was studied in mouse models that incorporated one or more disease characteristics associated with human CD:

- Presence of activated and expanding gliadin-specific T cells and/or,
- Intestinal disease (villous atrophy, crypt hyperplasia) and/or,
- Anti-gliadin antibody development.

In these studies mice received two intravenous (IV) administrations of TIMP GLIA, 7 days apart. TIMP-GLIA showed the potential to induce antigen specific T cell tolerance to gliadin, whether treatment preceded (prevention model) or followed (treatment model) animal sensitization to gliadin. The optimal active dose of TIMP-GLIA observed during these studies, 125 mg/kg, is the HED of 10.16 mg/kg.

The key elements and outcomes of these studies are summarized in Table 3. TIMP-GLIA was not found to bind anti-gliadin antibody.

In addition, the mouse tissues underwent histological examination for signs of potential Type III hypersensitivity. Type III hypersensitivity occurs when there is accumulation of immune complexes (antigen-antibody complexes) that are not adequately cleared by the mononuclear phagocyte system and instead accumulate in the kidneys where they trigger inflammatory changes. Histological evidence of recent or ongoing inflammation and complement deposition was not evident in the TIMP-GLIA treated mice.

Taken collectively the in vivo data supports the activity of TIMP-GLIA in physiologic systems involved in CD without untoward biologic effects at the proposed human doses.

1.3.2.3 Ex vivo Pharmacology (Human-Donor PBMCs)

Peripheral blood (from which PBMCs were harvested) was collected from healthy donors, donors with CD adhering to a GFD, and newly diagnosed celiac donors who were not adhering to a GFD. TIMP-GLIA incubation with PBMCs from these patients at concentrations as high as 1.25mg/mL (HED 100 mg/kg) did not cause T cell proliferation or pro-inflammatory cytokine production, indicating that the product is non-mitogenic.

Table 3. Summary of TIMP-GLIA Primary Pharmacology In Mouse Models

TIMP-GLIA induces immune tolerance without causing adverse immune response in a gliadin-induced DTH Model			
Model	**Purpose**	**Measures of treatment success**	**Outcomes**
Tolerance induction in gliadin-specific DTH mouse model	Show that two infusions of up to 125mg/kg (HED 10.16mg/kg) TIMP-GLIA induce T cell tolerance in mice when applied as prevention or treatment in gliadin immunized mice	1.Prevent gliadin induced ear swelling 2.Inhibit gliadin-specific T cell proliferation 3.Inhibit gliadin-specific T cell Interferon-γ	TIMP-GLIA induced antigen specific immune tolerance. 1.TIMP-GLIA resulted in antigen specific inhibition of gliadin induced ear swelling. 2.TIMP-GLIA resulted in inhibition of gliadin-specific T cell proliferation. 3.TIMP-GLIA resulted in inhibition of gliadin-specific T cell Interferon-γ .
No immune activation / adverse immune response in DTH mouse model	Show that two infusions of up to 125mg/kg (HED 10.16mg/kg) TIMP-GLIA do not activate or sensitize the immune system of mice when applied as prevention or treatment in gliadin immunized mice	1.Examine symptoms after two TIMP-GLIA infusions 2.Show no sensitization by looking at gliadin-specific antibody levels	1.TIMP-GLIA was not associated with adverse immune responses (anaphylaxis like) upon infusion. 2.TIMP-GLIA was not sensitizing, as it was not associated with anti-gliadin antibody production.
TIMP-GLIA induces immune tolerance and prevents gluten-induced intestinal pathology in adoptive transfer mouse model			
Model	**Purpose**	**Measures of treatment success**	**Outcomes**
Tolerance induction in gliadin induced intestinal autoimmune model (Adoptive transfer model)	Show that two infusions of up to 125mg/kg (HED 10.16mg/kg) TIMP-GLIA induce T cell tolerance in a mouse model of gluten induced intestinal autoimmunity (Rag adoptive transfer model).	Prevent gluten diet induced weight loss 1.Prevent gluten diet intestinal pathology 2.Inhibit gliadin-specific T cell proliferation 3.Inhibit gliadin-specific T cell Interferon-γ	TIMP-GLIA induced antigen specific immune tolerance. 1.TIMP-GLIA resulted in antigen specific prevention of weight loss. 2.TIMP-GLIA resulted in prevention from gluten induced intestinal pathology. 3.TIMP-GLIA resulted in inhibition of gliadin-specific T cell proliferation. 4.TIMP-GLIA resulted in inhibition of gliadin-specific T cell Interferon--γ
TIMP-GLIA induces immune tolerance in a mouse expressing human HLADQ8 and human CD4			
Model	**Purpose**	**Measures of treatment success**	**Outcomes**
TIMP-GLIA tolerance induction in transgenic mouse expressing celiac associated HLA DQ8 / huCD4	Show that two infusions of up to 125mg/kg (HED 10.16mg/kg) TIMP-GLIA induce T cell tolerance in a mouse expressing the common celiac HLA DQ8 and human CD4 can induce immune tolerance and modulate B cell responses.	1.Inhibit gliadin-specific T cell proliferation 2.Inhibit gliadin-specific T cell Interferon-γ 3. Prevent gliadin-specific antibody production	TIMP-GLIA induced antigen specific immune tolerance. 1.TIMP-GLIA resulted in inhibition of gliadin-specific T cell proliferation. 2.TIMP-GLIA resulted in inhibition of gliadin-specific T cell Interferon-γ. 3.TIMP-GLIA resulted in inhibition of anti-gliadin IgG2c levels.

DTH: delayed type hypersensitivity; Source: Investigator Brochure, Edition 1

1.3.3 Toxicology

Rats were chosen as the relevant toxicology species for TIMP-GLIA toxicology studies in collaboration with FDA. A non-GLP repeat dosage range finding study and the required GLP repeat-dose study were conducted with IV drug since this is the route intended for the Phase 1 administration.

1.3.3.1 Non-GLP Dose-Ranging Toxicology Study

TIMP-GLIA (Lot 36054) dosages used during the non-GLP study were 0, 10, 50, 75, 100, and 200 mg/kg (HED: 0, 1.6, 8, 12, 16, and 32 mg/kg) and administered IV on Days 1 and 8, with the necropsy being on Day 15 or Day 17 depending upon tissue/blood sampling requirements. In summary, TIMP-GLIA produced no significant toxicological or pathological effects at 10 mg/kg when administered IV on Days 1 and 8. A number of clinical pathology and microscopic histopathological effects were seen at dosages of > 50 mg/kg, predominately in the liver and the spleen. At 200 mg/kg two animals were euthanized due to drug-related effects. (See Table 4, Summary of Nonclinical Observations and Clinical Risk Minimization Actions, findings shown in italics font.)

Following the observation of liver pathology occurring in the high dose groups (> 50 mg/kg), a product purification change was implemented prior to formulating the TIMP-GLIA lot used in the pivotal GLP repeat dose toxicology study and all subsequent lots. This change provided for greater removal of small particulates by use of a higher cut-off filter (200 nm) than employed in the non-GLP material (50 nm). It is noteworthy that the adverse effects observed during the non-GLP toxicology study at doses ≥ 50 mg/kg were not observed during the GLP toxicology study (summarized below).

1.3.3.2 GLP Toxicology Study

TIMP-GLIA (Lot 36092) that had undergone the product purification mentioned above was administered IV to rats (10/sex/group) at dosages of 0, 4, 10, 50, and 75 mg/kg (HED: 0, 0.64, 1.6, 8, and 12 mg/kg). Infusions occurred on Days 1, 8, and 15 with the necropsy being on Day 16. An additional 5 rats/sex/group underwent the same dosing regimen followed by a 28-day recovery period after the last dose and necropsy on Day 43. Another 5 rats/sex/group were dosed on Day 1 and Day 8 and euthanized on Day 11 for pathology investigations and groups of 12 rats/sex/TIMP-GLIA group plus 6 /sex/control group were dosed on Days 1 and 8 for measurement of TGLIA-concentrations over time for TK analysis and for cytokine measurement. The animals in the TK/cytokine group were euthanized after the last blood draw.

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 a IV injection.

Several minor statistically significant changes were noted in the clinical pathology but were not judged by the study director to be drug-related as they were of insufficient magnitude or failed to show a relationship to dose. For example, a modest decrease was seen in total numbers of white blood cells (WBC) for the 75 mg/kg females at the recovery (Day 43) necropsy. This effect was judged to be of minimal toxicological significance because no corresponding effect was noted at the end of drug treatment necropsy (Day 16) or for the 75 mg/kg males at the end of the Recovery necropsy. Other observations from the GLP toxicology study are noted in Table 4, Summary of Nonclinical Observations and Clinical Risk Minimization Actions, findings shown in underline font.

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. 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 a IV injection.

The no observed adverse effect level (NOAEL) from this pivotal GLP toxicology study in rats was determined to be 75 mg/kg.

1.3.3.3 Non-GLP Follow-Up Study to GLP Toxicology Study

Because the NOAEL (75 mg/kg; HED 12 mg/kg) occurred at the maximum dose in the GLP toxicology study, a small scale follow up study testing 100 mg/kg (HED 16 mg/kg) and 150 mg/kg (HED 24 mg/kg) using the same TIMP-GLIA (Lot 36092) was performed in rats to characterize the toxicity profile at higher doses. TIMP-GLIA was administered as a slow bolus IV to rats (3/sex/group) at dosages of 0 (0.9% saline), 100, or 150 mg/kg (HED: 0, 16, 24 mg/kg) on Days 1 and 5 with daily clinical observations and laboratory testing (clinical chemistry, coagulation, hematology) and histopathology performed on Days 4 and 8. Necropsy occurred on Day 9.

All animals survived until euthanasia for necropsy and no abnormal clinical behaviors were observed. Findings are presented in Table 4. Summary of Nonclinical Observations and Clinical Risk Minimization Actions. As previously observed, liver and spleen were the target organs of toxicity. 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.

TIMP-GLIA-related effects were noted on clinical chemistry and hematology tests and generally were mild or moderate. Histopathological findings in the liver included dose-dependent minimal to moderate mononuclear sinusoidal infiltrates and non-dose dependent minimal to mild increased hematopoiesis (females only) and at 150 mg/kg included minimal increased mitosis in hepatocytes

and minimal biliary hyperplasia. Findings correlated with laboratory changes. Histopathological findings in the spleen included dose-dependent minimal to moderate increased cellularity (mononuclear) in the red pulp and marginal zone and minimal to moderate increased hematopoiesis. Effects at 150 mg/kg included minimal to mild decreased marginal zone lymphocyte cellularity. Spleen effects correlated with macroscopic observation of increased spleen weight/enlargement and laboratory changes.

These data are consistent with prior observations and do not change safety conclusions.

1.4 Clinical Studies

To date no clinical studies of TIMP-GLIA have been conducted.

1.5 Benefit-Risk Assessment

The subjects participating in this first-in-human (FIH) study will not benefit directly from administration of TIMP-GLIA. Subjects may derive satisfaction from their contribution towards the development of a potential new treatment for CD.

In contrast, subjects may experience adverse events (AEs) related to study drug, including exposure to residual trace amounts of non-particle-associated gliadin protein present within the reconstituted TIMP-GLIA drug product. Subjects may experience procedural complications related to blood draws or infusion including infusion-related reaction (IRR), and/or slight skin irritation from the adhesive of the electrocardiogram (ECG) electrodes. Risk of anaphylaxis/anaphylactoid response, characterized by rapid induction of proinflammatory cytokines and accompanied by headache, dyspnea, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension, with subsequent life-threatening lung injury, renal failure, and disseminated blood clots (Suntharalingam 2006) is not probable based upon the nonclinical data and observations whereby gliadin exposure does not induce anaphylaxis. Notwithstanding, this risk cannot be entirely ruled out.

At the time of this amended protocol (Version 9), TIMP-GLIA has been given as a single infusion to 17 subjects with celiac disease (Part A of this study). At the highest dose tested, approximately 650 mg, 2 of 4 subjects experienced a moderate IRR. For one of the subjects the infusion was stopped and the signs and symptoms went away immediately. For the second subject, the infusion was stopped and the signs and symptoms went away immediately, and the infusion was restarted at a slower rate. The subject completed the infusion without any other problems.

Signs and symptoms of IRR to TIMP-GLIA have included flushing (warm feeling or reddening of face, back and/or chest), rash, nausea, vomiting, back pain, low or high blood pressure, or increase in heart rate. These symptoms were either mild or moderate. All symptoms started within 2 minutes of the infusion starting and went away very quickly when the infusion was stopped or interrupted.

A conservative approach is being implemented to minimize risks to subjects in the first-in-human (FIH) study. Safety precautions are included in the design to address all findings observed during nonclinical studies, even those observed in the non-GLP toxicology study that were not observed

during the GLP toxicology study. A summary of nonclinical observations and the strategy to mitigate the risk are summarized in Table 4.

The sponsor believes that the potential for immunoreactivity and anaphylaxis/anaphylactoid response by subjects in this FIH trial is low based on the following characteristics and findings for TIMP-GLIA:

- The key components of TIMP-GLIA are PGLA polymer and gliadin.
    - PLGA is a biodegradable (hydrolyzed to its original monomers, lactic acid and glycolic acid) and biocompatible component of 15 FDA-approved products. These products have demonstrated minimal systemic toxicity associated with PLGA for drug delivery or biomaterial device applications (Makadia 2011, Wang 2016).
    - Gliadin is prolamin protein that is the same as occurs in wheat-containing foods ingested by healthy individuals or intentionally or unintentionally ingested by patients with CD, or administered during gluten challenge studies (Anderson 2005, Han 2013, Leffler 2013).
- TIMP-GLIA decreased antigenic response during nonclinical studies. TIMP deliver the gliadin antigen via natural phagocytosis of the PLGA particles, a noninflammatory process. Following this, nonclinical data showed treatment- induced production of the regulatory cytokines IL-10 and TGF-β in the spleen as well as upregulation of inhibitory ligands on macrophages, such as programmed death-1 (PD-1). Downstream events included the induction of T cell anergy and the activation of regulatory T cells (Getts 2015).
- There is low expectation of an IgE-mediated (classic anaphylaxis) or IgG-mediated anaphylaxis in subjects treated with TIMP-GLIA. IgE-mediated anaphylaxis results from cross linking of protein-specific antibody bound to mast cells/basophils. This is highly unlikely because CD is characterized by gliadin-specific IgG, not IgE, and subjects with wheat allergy (which is IgE-mediated) are excluded from participation. Furthermore, there is little surface protein on the TIMP-GLIA particle that can bind to any gliadin-specific receptor (of IgE or IgG isotype), whether circulating or bound to mast cells.
- In vitro studies with peripheral blood mononuclear cells from healthy donors and donors with celiac disease show that TIMP-GLIA does not cause T-cell proliferation or proinflammatory cytokine production, indicating the product is not mitogenic in either population. TIMP-GLIA does not interact directly with the T cell receptor (TCR) nor does it cause activation of T cells through binding of co-stimulation molecules expressed on T cells, platelets and other leukocytes. TIMP-GLIA regulates gliadin specific T cells indirectly, through antigen presenting cells. Therefore, TIMP-GLIA is unlikely to trigger positive co-stimulatory molecule activation (as observed with TGN1412) and potential for cytokine storm is very low.

Although the characteristics of TIMP-GLIA suggest a downregulation of immune response, the study design features and safety precautions to be implemented during the study will minimize medical risk to the subjects. These include:

- TIMP-GLIA will be administered IV, the route generally considered to be the least likely to elicit an immune response compared to intradermal, subcutaneous, and inhalational routes of administration.

- A safe starting dose was calculated taking into consideration the no observed adverse effect level (NOAEL) from the GLP toxicology study and the pharmacologic activity observed during the in vivo mouse study of DTH (see Section 2.5 Rationale for Dose Selection).
- Subjects will be carefully screened for participation in the trial. Subject enrollment will be limited to those who are otherwise healthy or who have stable comorbidity in compliance with the study-specific inclusion and exclusion criteria.
    - Subjects who have a history of allergic reaction to wheat or who have a known hypersensitivity or allergies to the TIMP-GLIA excipients (as specified in the investigator brochure), or who have any other history of severe hypersensitivity or allergic reaction to any allergen are excluded from participation in the study.
    - Subjects with cardiac conduction abnormalities or clinically significant laboratory test results (e.g., cell counts, LTs, INR) will be excluded.
- This study will be conducted in clinical research units with adequate equipment and staff training to manage clinical emergencies (crash carts) and proximity to hospital emergency departments for rapid delivery of urgent care.
- Subjects will be resident in the clinic for continuous medical monitoring for 48 hours after dosing. Prior to clinic discharge subjects will be evaluated medically including review of safety laboratory results from samples collected 24 hours post dose including electrolytes, white blood cell counts with differential, coagulation (see Table 9. Clinical Laboratory Tests) and occurrence of AEs including clinically significant cardiovascular (safety ECG)-, renal-, gastrointestinal- and CNS-related symptoms. Discharge may be delayed if the investigator determines additional medical follow up is necessary. Follow up assessments will be conducted on an outpatient basis or by telephone (see the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS
- Table 1) and Part B (Table 2) and unscheduled in-clinic visits and laboratory tests may be performed as needed to follow-up suspected AE(s).
- Part A of the protocol TGLIA-5.001 uses a staggered dosing strategy across sites. One subject in a cohort will be dosed at a time, and undergo medical observation in the clinic for at least 48 hours. Seven days (168 hours) will elapse before the next subject will be dosed at the same level.
- For Part B, subjects within a cohort may be enrolled/dosed concurrently.
- If none of the subjects in the cohort experiences a dose-limiting toxicity and stopping criteria ("Study Stopping Rules") are not met based upon Data Monitoring Committee (DMC) assessment of accumulating safety data, then escalation to the next higher dose may proceed. However, if 1 of the subjects at a dose level exhibits a dose-limiting toxicity, additional subject(s) will be dosed at the same level to clarify ambiguous safety findings.
- In Part A, when all subjects in a dose cohort complete procedures through 168 hours post dose, the overall safety and tolerability data (AEs, vital signs, 12-lead ECGs, clinical laboratory tests, cytokines) for the current cohort and available cumulative AE data from previous cohorts will be reviewed by the DMC who will determine the progression or termination of dosing. In Part B, the DMC will review all safety date from a cohort when the last subject in a cohort has completed procedures through 48 hours.

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A summary of nonclinical risk factors and the strategy to mitigate the risk are summarized in Table 4. Taken collectively, the nonclinical data and drug characteristics suggest that there are no undue risks to subjects who participate in this FIH study.

Table 4. Summary of Nonclinical Observations and Clinical Risk Minimization Actions

Target	Species	All Observations† From *non-GLP* (italics) and GLP (underlined) toxicology, or in vitro NCL panel	Risk Minimization Action
Liver	Rat	↑*ALT; ↑AST; ↑ALP; ↑GGT; ↑bilirubin; ↑triglycerides; hepatocellular necrosis & congestion; red discoloration of the liver; hepatic infiltrates; ↓cholesterol, ↑cholesterol; ↓albumin; ↓fibrinogen; also ↑fibrinogen; prolonged aPTT and PT; Kupffer cell erythrophagocytosis* hepatocellular necrosis (n=1); ↑ALT; ↑triglycerides; ↓total bilirubin; ↓PTT; ↑fibrinogen <*↑fibrinogen; ↑ALT; ↑AST; ↑ALP; ↑GGT; ↑bilirubin; mononuclear sinusoidal infiltrates and ↑hematopoiesis; ↑mitosis in hepatocytes; biliary hyperplasia*>	Standard liver function tests; coagulation tests, monitor CTCAE Investigations and Hepatobiliary AE; Subjects with clinically significant abnormal LFTs, coagulation tests are excluded from participation.
	In vitro	Prolonged aPTT, TT; ↓reactive oxygen species; ↑apoptosis	
Kidney	Rat	↑*BUN; renal medulla tubular necrosis; granular casts; tubular dilatation*	Standard chemistry and urinalysis; monitor CTCAE Investigations & Renal and Urinary Disorders AEs; Subjects with clinically significant laboratory results or baseline conditions are excluded from participation.
Electrolytes /metabolic	Rat	↓*glucose*	Standard chemistry and urinalysis; monitor CTCAE Investigations & Metabolism & Nutrition Disorders AEs; Subjects with clinically significant laboratory results or baseline conditions are excluded from participation.

Table 4 *continued next page.*

CTCAE: Common terminology criteria for adverse events

† All clinical pathology and gross/histopathology findings are noted even if deemed biologically non-significant /minimal /mild; thought to be an NCL assay artifact; observed only at ↑dose relative to planned clinical doses; OR observed only with the non-GLP manufacturing batch of drug and the effect was not observed during GLP toxicity study.

Following the non-GLP toxicology study, a product purification change was implemented prior to formulating the TIMP-GLIA lot used in the pivotal GLP repeat dose toxicology study and all subsequent lots. This change provided for greater removal of small particulates via a higher cut-off filter (200 nm) than employed in the non-GLP material (50 nm).

< > Denotes new data from a *non GLP* toxicology study TGLIA-1.039 which were available after the Investigator's Brochure and original TGLIA-5.001 protocol were finalized. These data are consistent with prior observations and do not change safety conclusions.

Table 4. Continued, Summary of Nonclinical Observations and Clinical Risk Minimization Actions

Target	Species	All Observations† From non-GLP (italics) and GLP (underlined) toxicology, or in vitro NCL panel	Risk Minimization Action
Hematopoietic system	Rat	*↑Reticulocytes; ↓red cell mass (RBC, HGB, Hct); ↑RBC distribution width; ↓platelets; ↑neutrophils, ↑monocytes, ↑basophils, and ↑eosinophils;* also *↓eosinophils and ↓basophils; ↑lymphocytes; ↑immature hematopoietic precursors; ↑hematopoiesis in liver and spleen and bone marrow; enlargement of spleen; ↓lymphoid cellularity of marginal zone; ↓cellularity and/or apoptosis of lymphoid cells in non-spleen lymphoid tissue; dark color of mesenteric lymph nodes; capsular fibrosis; 1+ to 3+ numbers of band neutrophils and Dohle bodies on blood smear* ↓WBC; ↓neutrophils; ↓eosinophils; ↑monocytes; ↓lymphocytes; ↓platelets; ↑reticulocytes; ↑MCV; ↑RBC distribution width; ↓MCHC; ↓spleen weight <*↑Reticulocytes; ↓red cell mass (↓RBC ↓HGB ↓Hct); ↑RBC distribution width; ↑WBC; ↑monocytes; ↑neutrophils; ↑spleen weight/spleen enlargement; microscopic findings of ↑hematopoiesis and infiltrates of mononuclear cells; ↑cellularity (mononuclear) in the red pulp and marginal zone; ↓marginal zone lymphocyte celluarity*>	Standard hematology laboratory parameters including MCV, RBC, and reticulocytes; monitor CTCAE Investigations AEs; Subjects with clinically significant abnormal laboratory results or baseline conditions are excluded from participation.
Cardiovascular system	Rat	*Cardiac myofiber necrosis and hemorrhage*	Telemetry 8 hours post dose; serial ECGs post dose compared to predrug baseline triplicates; monitor CTCAE Cardiac Disorders AEs; Subjects with abnormal, clinically significant screening ECG or baseline conditions are excluded from participation.
Other	Rat	*Dark foci of the lungs/congestion; Type 2 pneumocyte hypertrophy within lungs; epithelial necrosis of glandular stomach; epithelial apoptosis and/or atrophy of various tissues, including epididymis*	Physical exam, monitor CTCAE AEs; birth control requirement during study

CTCAE: Common terminology criteria for adverse events

† All clinical pathology and gross/histopathology findings are noted even if deemed biologically non-significant /minimal /mild; thought to be an NCL assay artifact; observed only at ↑dose relative to planned clinical doses; OR observed only with the non-GLP manufacturing batch of drug and the effect was not observed during GLP toxicity study.

Following the non-GLP toxicology study, a product purification change was implemented prior to formulating the TIMP-GLIA lot used in the pivotal GLP repeat dose toxicology study and all subsequent lots. This change provided for greater removal of small particulates via a higher cut-off filter (200 nm) than employed in the non-GLP material (50 nm).

< > Denotes new data from a *non GLP* toxicology study TGLIA-1.039 which were available after the Investigator's Brochure and original TGLIA-5.001 protocol were finalized. These data are consistent with prior observations and do not change safety conclusions.

2 STUDY DESIGN AND RATIONALE

2.1 Overview of Study Design

This study is a Phase 1, FIH, 2-part, multicenter study to assess the safety, tolerability and pharmacokinetics (PK) of TIMP-GLIA in subjects with CD. Part A includes an accelerated titration 2+2 and traditional 3 + 3 design with rapid dose escalationduring which successive cohorts of subjects will receive a single dose of TIMP-GLIA. Part B will follow as a repeat dose design using the dose level selected from Part A. (See **Error! Reference source not found.**, **Error! Reference source not found.**.)

Consenting subjects will be screened within 28 days (Day -28 to -1) prior to admission to the clinical research unit on Day -1 for baseline assessments.

Part A

In Part A, eligible subjects (at least 19 subjects) will be enrolled into escalating dose cohorts (n = 2/cohort for 2 dose levels followed by n = 3/cohort for 5 dose levels). TIMP-GLIA will be administered as a single IV infusion on Day 1. A staggered dosing strategy will be used in Part A. One subject in a cohort will be dosed at a time and undergo medical observation in the clinic for at least 48 hours post-infusion.

At least 168 hours (7 days) will elapse prior to dosing the next subject. AEs, vital signs, pulse oximetry, and ECGs and laboratory data (serum chemistry, coagulation, hematology and urinalysis, cytokines) from samples obtained through at least 24 hours post dose will be assessed before dosing the subsequent subject(s).

AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Published: May 28, 2009 [v4.03: June 14, 2010]) or most current version. If safety and tolerability are confirmed by the investigator, TIMP-GLIA will be administered to the next subject.

Dose Escalation, Part A

After all the subjects in a dose cohort complete study procedures through at least 168 hours (7 days) post dose the safety data by the DMC. Dose escalation will proceed only if Study Stopping Criteria ("Study Stopping Rules") are not met. If dose-limiting toxicity occurs in 1 of the subjects in the cohort, the DMC may decide to increase enrollment at the same dose level by 2 subjects (accelerated titration cohort) or by 3 subjects (standard 3+3). After a rate of DLTs has been identified for a specific dose in 3- or 6-subject cohorts, the DMC may recommend that up to a total of 12 subjects may be accrued at any dose level to better define the relationship between dose and emerging the safety signals. It is also possible that the DMC could recommend an intermediate dose (lesser escalation) or reduced dose level (dose reduction) if warranted by the emerging safety data. Before continuing to Part B, available safety data for all subjects in Part A through at least 168 hours (7 days) after dosing will be evaluated by the DMC.

Part B

Part B will evaluate 2 doses of TIMP-GLIA administered on Days 1 and 8. Two subjects will be enrolled into each of 3 cohorts at dose levels of 2, 4, and 8 mg/kg up to a maximum of 650 mg. Dose escalation will proceed only if Study Stopping Criteria ("Study Stopping Rules") are not met. If dose-limiting toxicity (DLT) occurs in 1 of the 2 subjects in a cohort, the DMC may decide to increase enrollment at the same dose level by 2 subjects. (2+2 design).

Clinic Residency and Visits

Subjects in both parts of the study will remain in the clinic from admission (Part A: Day -1; Part B: Day -1 and Day 7)) through the final post-dose procedure at 48 hours (Part A: Day 3; Part B: Day 3 and Day 10) and will be thereafter discharged if safety parameters are acceptable to the investigator. Subjects will return to the clinical research unit for follow-up assessments or may be contacted by telephone as shown in the *Schedules of Procedures* for each part of study.

Duration of Study

Part A: Total duration of the study investigational period is up to 91 days (screening up to 28 days + 1 treatment day + follow-up at Day 60 +/- 3 days). In addition, telephone follow-up by a health care practitioner is required after the Day 60 outpatient visit (i.e., Day 90, Day 120, Day 180, all +/- 3 days).

Part B: Total duration of the study investigational period is up to 91 days (screening up to 28 days + 2 treatment days, 7 days apart + follow-up at 60 +/- 3 days after last dose). In addition, telephone follow-up by a health care practitioner is required after the Day 60 outpatient visit (i.e., Day 90, Day 120, Day 180, all +/- 3 days).

2.2 Rationale for the Trial

This study is being conducted to obtain initial safety, tolerability, and pharmacokinetic information of single and repeat IV doses of TIMP-GLIA in adult subjects with CD. Nonclinical pharmacology data with TIMP-GLIA have suggested a mechanism of action relevant to the pathophysiology of CD. In the mouse model of CD, TIMP-GLIA has been shown to induce T cell tolerance by systemically targeting and controlling, gluten-reactive T cells. (See Investigator's Brochure.) Since T cell activation is considered to be the major cause of the mucosal inflammation, consequent antibody production, and tissue destruction observed in CD, further evaluation of a therapeutic agent capable of specifically inactivating, or tolerizing, these gliadin specific T cells is warranted. Results from the GLP repeat dose toxicology study in rats has raised no safety concerns associated with TIMP-GLIA administration but appropriate precautions will be engaged to protect and evaluate subject safety after single and repeat (2) doses of TIMP-GLIA.

2.3 Rationale for the Trial Design

This FIH clinical study in patients with stable CD will consist of 2 parts. Part A is a traditional, open-label, single ascending dose (SAD) study with staggered dosing. The dose escalation and cohort size in Part A are based upon accepted methodology for phase I studies (Le Tourneau 2009, Rubinstein 2003). In Part A, an accelerated titration (2+2) model will be followed at the lowest

doses followed by the standard 3+3 model at higher doses. In Part B, an accelerated titration (2+2) model will be followed. See also Figure 1. Schematic of Planned Dosing in Subjects With Celiac Disease, Part A and Part B and further description in Section 2.1, Overview of Study Design.)

In Part A, this design will allow the study proceed more quickly through the lowest doses at which little or no effect is anticipated to be observed. Cohort size increases to 3 at the doses for which pharmacologic or clinical effect would be more likely, based upon the nonclinical studies. The cohort size in the accelerated titration phase of 2 subjects and an additional 2 subjects if warranted, and the cohort size in the standard 3+3 phase of at least 3 and up to 6 subjects if warranted, have been employed to facilitate a reasonable rate of accrual of subjects and to confirm ambiguous safety or tolerability findings. In Part B, the accelerated model allows the study to proceed at the lower doses at which little or no affect is expected.

Subject safety is prioritized at all doses.

Should a dose limiting toxicity (DLT) occur in one subject, an additional cohort will be dosed at the same dose level to follow up ambiguous safety observations, provided no stopping criteria ("Study Stopping Rules") have been met according to the DMC (see Section 7.2, Safety Committee). Stopping criteria have been set in accordance with traditional phase I study methodology. Decisions to advance or modify dose level(s) within Part A will be guided by evaluation of accumulating safety and tolerability data by the DMC.

Part B will be a repeat-dose study with 2 subjects who will receive the first infusion on Day 1 and the second infusion on Day 8. If a dose-limiting toxicity occurs in 1 of the 2 subjects in Part B, the DMC may decide to enroll an additional 2 subjects at the same dose to confirm ambiguous safety or tolerability findings. Repeat dosing will provide support for safe and tolerable dosing using the 2-dose regimen to be investigated in the future proof-of-concept (POC) clinical trial.

The 48-hour minimum observation period prior to discharge was selected because the major potential toxicities are anticipated to emerge within this duration.

The Day 60 (+/- 3 days) outpatient follow-up visit of the investigational period and Day 180 (+/- 3 days) telephone contact follow up after last dose will allow sufficient time to capture potential delayed-onset AEs and evaluate the potential for antibody response to TIMP-GLIA.

2.4 Rationale for the Subject Population

The rationale for going directly into the subject population of interest (CD subjects) in this first-in-human (FIH) study is to allow early assessment of any disease-specific safety issues and is supported as follows:

- CD is characterized by an immune reaction to the gliadin component of gluten. Only celiac patients have gliadin-specific T cells. (Anderson 2000, Han 2013, Christophersen 2016) As the mechanism of action of TIMP-GLIA involves gliadin-specific T cells, the potential drug effects on T cells cannot be measured in healthy individuals, only those reactive to gluten. In other words, healthy individuals are tolerant to gluten and as such data obtained from studies using healthy subjects may provide incomplete information/conclusions regarding

TIMP-GLIA safety. Thus, subjects with CD provide the most likely opportunity to determine any potential adverse safety signal in the presence of gliadin-specific T cells.

- CD patients on a GFD provide the best opportunity to measure PK of TIMP-GLIA without the potential for confounding background levels of gliadin.
- Restricting enrollment to subjects with negative celiac serology and quiescent CD symptomology (clinically inactive) who are otherwise healthy or with stable comorbidity will minimize the potential to confound the interpretation of safety data.
- Excluding subjects with history of immunoglobulin E (IgE)-mediated reaction and/or anaphylaxis to wheat (i.e., "wheat allergy"), barley or rye or a known history of hypersensitivity or allergies or severe allergic reaction to any other allergens (medications, food or environmental) is a safety precaution.

2.5 Rationale for Dose Selection

The determination of the planned starting dose of this study and the dose range to be tested is consistent with the principles set out in FDA 2005 *Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (FDA July 2005) and FDA 2011 *Guidance for Industry Clinical Considerations for Therapeutic Cancer Vaccines* (FDA October 2011). The rationale for determining a safe starting dose for the FIH study takes a multi-faceted approach considering all of the data and experience obtained during nonclinical studies, summarized previously. The maximum recommended starting dose (MRSD) was determined conservatively, taking into account both the NOAEL in rat GLP toxicology study and the pharmacologically active doses (PAD) causing partial inhibition and full inhibition of ear swelling in a mouse DTH model pharmacology study; to these a ten-fold safety margin was applied.

The findings from the in vivo nonclinical pharmacology and toxicology studies of TIMP-GLIA have provided reasonable assurance that there are no undue risks for the first administration of TIMP-GLIA to humans at the dose levels proposed in this study.

2.5.1 TIMP-GLIA Toxicology and the NOAEL

The GLP repeat-dose toxicology study of TIMP-GLIA is required by FDA to assess toxicity in the appropriate animal model (rat). This GLP study also utilized TIMP-GLIA formulation that underwent the additional purification step that is applicable to the clinical lots. For these reasons, the NOAEL has been identified from the GLP toxicology data for calculation of the maximum recommended starting dose ($MRSD_{tox}$) for the FIH trial.

Upon evaluation of the GLP toxicology data (Section 1.3.3.2, GLP Toxicology Study and Investigator Brochure, Edition 1), the study director identified a NOAEL of 75 mg/kg.

Using both standard conversions (by body surface area and body weight) described in the FDA 2005 Guidance for Industry, the $MRSD_{tox}$ based upon NOAEL in rat is calculated as shown in Table 5.

Table 5. Calculations of Maximum Recommended Starting Dose Based upon Toxicology (NOAEL) Data

NOAEL Apply animal-to-human conversion factor **HED_{tox}** Apply 10-fold safety **$MRSD_{tox}$**	**Step 1: Determination of NOAEL in most sensitive animal species** NOAEL in Rat: 75 mg/kg/day	
	Step 2:Conversion of Animal Dose to HED	
	Body surface area conversion **Conversion of Rat Dose in mg/kg to mg/m²** $[75\ mg/kg]_{NOAEL} \times [6\ kg/m^2]_{Rat\ Conv\ Factor} = 450\ mg/m^2$ **Conversion of Rat Dose in mg/m² to HED in mg/kg, assuming 60 kg human with mean BSA of 1.79 m²** $450\ mg/m^2 \times 1.79\ m^2 = 805.5\ mg \div 60\ kg = 13.4\ mg/kg$*	Body weight conversion **Conversion of Rat Dose in mg/kg to HED in mg/kg assuming a 60 kg human** $[75\ mg/kg]_{NOAEL} \times [.162]_{Rat\ Conv\ Factor} = 12.1\ mg/kg$* Or $[75\ mg/kg]_{NOAEL} \div [6.2]_{Rat\ Conv\ Factor} = 12.1\ mg/kg$*
	*NOAEL rounded down to 10.0 mg/kg	
	Step 3: Apply 10-fold safety factor	
	$10.0\ mg/kg \div 10 = 1.0\ mg/kg$	

HED: Human Equivalent Dose; BSA: body surface area

2.5.2 TIMP-GLIA Pharmacologically Active Dose

TIMP-GLIA pharmacologic effect was evaluated in vivo using a mouse model of DTH. Mice were treated with two infusions of TIMP-GLIA after sensitization with gliadin (Table 3). Pharmacologic activity was initially observable at 12.5 mg/kg as partial inhibition of gliadin-specific inflammation (ear swelling) comparted to non-treated controls ("subtherapeutic response"). Full inhibition ("therapeutic response") was observed at 125 mg/kg compared to non-treated controls. This is the relevant dose range of TIMP-GLIA pharmacologic activity (pharmacological active dose, PAD).

Applying the standard conversions (by body surface area or body weight) described in the FDA 2005 Guidance for Industry to the TIMP-GLIA doses, $MRSD_{PAD}$ based upon full or partial inhibition of DTH response is calculated as shown in Table 6.

Table 6. Calculations of Maximum Recommended Starting Dose Based upon Pharmacologically Active Dose for Full and Partial DTH Inhibition

PAD	**Step 1: Determination of PAD in relevant animal model** PAD in Mouse, partial inhibition of DTH: 12.5 mg/kg/day PAD in Mouse, complete inhibition of DTH: 125 mg/kg/day	
Apply animal-to-human conversion factor	**Step 2:Conversion of Animal Dose to HED**	
	Body surface area conversion	Body weight conversion
	Conversion of Rat Dose in mg/kg to mg/m² $[12.5\ mg/kg]_{Partial\ inhibition} \times [3\ kg/m^2]_{Mouse\ Conv\ Factor} = 37.5\ mg/m^2$	**Conversion of Rat Dose in mg/kg to HED in mg/kg assuming a 60 kg human** $[12.5\ mg/kg]_{Partial\ inhibition} \times [.081]_{Mouse\ Conv\ Factor} = 1.02\ mg/kg$
HED_{PAD}	**Conversion of Rat Dose in mg/m² to HED in mg/kg, assuming 60 kg human with mean BSA of 1.79 m²** $37.5\ mg/m^2 \times 1.79\ m^2 = 67.12\ mg \div 60\ kg = 1.12\ mg/kg$	Or $[12.5\ mg/kg]_{Partial\ inhibition} \div [12.3]_{Mouse\ Conv\ Factor} = 1.02\ mg/kg$
Apply 10-fold safety factor Select lowest	Corresponding HED for $[125\ mg/kg]_{Complete\ inhibition}$ is 11.2 mg/kg.	Corresponding HED for $[125\ mg/kg]_{Complete\ inhibition}$ is 10.2 mg/kg.
$MRSD_{PAD}$	**Step 3: Apply 10-fold safety factor**	
	1.12 mg/kg ÷ 10 = 0.11 mg/kg	1.02 mg/kg ÷ 10 = 0.10 mg/kg
	11.2 mg/kg ÷ 10 = 1.12 mg/kg	10.2 mg/kg ÷ 10 = 01.0 mg/kg

HED: Human Equivalent Dose; BSA: body surface area

In addition to the in vivo toxicology and DTH data, TIMP-GLIA was studied for its potential to induce T cell proliferation / mitogenicity in a Phase 0 ex vivo study using peripheral blood mononuclear cells (PBMCs) from human donors: healthy subjects, celiac subjects adhering to a GFD, and subjects newly diagnosed with CD who were not yet adhering to a GFD. Subjects with CD adhering to a GFD are most representative of the subjects to be enrolled in the Phase 1 clinical study.

T cell mitogenicity was not observed from samples collected from any of the subject cohorts up to the maximum concentration studied of 1.25 mg/mL (HED ~100 mg/kg assuming a 70 kg human with 5.6 L of blood volume using the conversion method described in NCL in vitro study protocols). In addition, no immune cytokine activation was observed in the samples from the human donors. Based upon this result, immune activation may only be anticipated to occur at some level greater than ~100 mg/kg.

2.5.3 TIMP-GLIA Maximum Recommended Starting Dose

Applying the most conservative approach for the FIH clinical study, a starting dose of 0.1 mg/kg followed by 0.5 mg/kg will be explored in 2 subjects each via an accelerated titration 2 + 2 schedule. This is followed by dosing cohorts of 3 subjects according to a standard 3+3 escalation schedule beginning with a dose of 1 mg/kg. The larger cohorts are employed at 1 mg/kg when pharmacologic effects are more likely to be observable.

The planned doses and escalation schedule are illustrated in Figure 1. Schematic of Planned Dosing in Subjects With Celiac Disease, Part A and Part B and listed below Table 7.

Table 7. Planned Dose Levels and Rationale

	Part A	Single dose mg/kg	Rationale
Accelerated Titration 2 + 2	Level 1	= 0.1	100x below NOAEL 10x below PAD for initial pharmacologic activity
	Level 2	= 0.5	20x below NOAEL
Standard 3+3	Level 3	= 1.0	10x below NOAEL At PAD for initial pharmacologic activity
	Level 4	= 2.0	2x escalation
	Level 5	= 4.0	2x escalation
	Level 6	= 8.0	2x escalation
	Level 7	= 10.0 or a maximum of 750 mg Not administered; CCI [redacted]	At PAD for complete inhibition of DTH

	Part B	Repeat dose mg/kg	
Accelerated Titration 2 + 2	Level 1	2 mg/kg	
	Level 2	4 mg/kg	
	Level 3	8 mg/kg to a maximum of 650 mg	Maximum dose found to be safe and tolerable in Part A

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

The primary objective is to assess the safety and tolerability of TIMP-GLIA when administered IV as a single dose at ascending dose levels and as a repeat dose in subjects with CD.

3.1.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of TIMP-GLIA based upon concentrations of TIMP-GLIA in plasma over time in subjects with CD.
- To establish a safe and tolerable dose that may be tested during a future Phase 2 Proof of Concept study in subjects with CD.

3.1.3 Exploratory Objective

CCI [redacted]

3.2 Endpoints

3.2.1 Safety and Tolerability Endpoints

Safety will be characterized by incidence, severity, and reversibility of AEs, physical examination findings, 12-lead ECG results, arterial oxygen saturation levels by pulse oximetry, vital signs measurements, anti-gliadin antibody (i.e., anti-drug antibody as deamidated gliadin peptide (DGP)-specific IgG), immune complex detection by C1q binding and by C3a and SC5B-9 (Part B only), routine clinical laboratory test results (hematology, serum chemistry, coagulation, urinalysis) and other specialized laboratory test results (e.g., acute phase cytokines; additional vascular / thrombotic markers; mast cell activation via tryptase; additional complement markers, peripheral blood gliadin-specific T-cell proliferation and cytokine secretion). Post-dose assessment of peripheral blood T cell proliferation and cytokine secretion in response to ex vivo gliadin stimulation relative to baseline, will be performed for the single dose groups ≥ 4 mg/kg in Part A and for the repeat dose groups in Part B.

The analysis of samples drawn for cytokine testing (EGF, fractalkine, GM-CSF, GRO α, IFNα, IFN-γ, IL-1α, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, , IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, MIP1α, and MIP1β, TNF-α)should be performed as described in Section 8.5.6.5, *C3a and SC5B-9 Complement Levels*

For Part B, C3a and SC5B-9 complement levels will be obtained during the infusion and 24 hours following the infusion (refer to Table 2. Schedule of Procedures, Part B).

Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction.

Results of peripheral blood T-cell proliferation and cytokine secretion in response to ex vivo stimulation with gliadin following exposure to TIMP-GLIA assay is performed, results will be reported at the end of the study or as otherwise specified by the sponsor, medical monitor, or DMC.

Tolerability will be characterized by extent of dose escalation attained without dose limiting toxicity.

3.2.2 Pharmacokinetics Endpoints

The PK of TIMP-GLIA will be derived from the plasma TIMP-GLIA concentration – time curve by noncompartmental analysis. The primary PK parameters are maximal observed concentration (C_{max}), last measurable concentration (C_{last}), time of maximal observed concentration (T_{max}), and area under the curve from time zero and extrapolated to infinity (AUC_{inf}) and area under the concentration-time curve from time zero to time of the last measurable concentration (AUC_{last}). Other PK variables will be derived if feasible. The results of the PK evaluation will be reported at the end of the study.

Establishment of a maximal feasible dose (MFD) to administer during the future proof-of-concept study in CD patients is another secondary endpoint.

4 STUDY POPULATION

At least 23 male and female subjects 18 to 75 years of age with historical evidence of biopsy-confirmed CD and who have negative celiac serology and quiescent CD symptomology and are otherwise healthy or with stable comorbidity at screening are planned to be enrolled. Subjects will be enrolled at up to 6 clinical research sites in the United States.

Subjects who withdraw before receiving the first dose of study drug will be replaced. Subjects who withdraw after receiving study drug will be replaced at the sponsor's discretion.

After fully informing prospective subjects of the present study and obtaining their written informed consent, the investigator will perform screening tests. Based on the results of these screening tests, the investigator will identify "provisional subjects" (including reserve ["alternate"] subjects, if available). The provisional subjects will be individuals who meet the inclusion criteria without meeting any of the exclusion criteria. Ethical and scientific aspects, the study objectives, and individual health status up to the selection date will also be carefully considered during the selection process. The provisional subjects, if available, will be admitted to the study site on the day on Day -1, whereupon they will undergo the tests scheduled for that day and confirmatory assessment of study eligibility criteria. Those who are deemed eligible for enrollment will then be selected as enrolled subjects (including reserve subjects).

There will be no waivers or exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

4.1 Inclusion Criteria

A subject must meet all the following criteria to qualify for entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject provided written informed consent to participate as indicated by a signature on the informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is an adult man or women, 18 to 75 years of age, inclusive, at Screening Visit.
4. The subject has a body mass index (BMI) that is >16 kg/m2 and with a minimum body weight of 33 kg up to a maximum body weight of 129 kg, inclusive, at Screening Visit and if BMI <18 ("underweight") or >25 ("overweight" or "obese"), is otherwise healthy in the opinion of the investigator.
5. The subject has celiac disease characterized as follows:
    a. The subject has a history of biopsy-confirmed celiac disease (intestinal histology showing villous atrophy) according to expert guidelines current at the time of diagnosis; and
    b. The subject has no known gluten exposure for at least 10 days prior to the Screening Visit and is willing to maintain a gluten-free diet for the duration of the study; and

c. The subject has a total immunoglobulin A (IgA) titer within normal limits or has partial IgA deficiency (~5% of celiac patients) defined by a reduced serum IgA level of 3 – 70 mg/dL at Screening
AND
The subject has negative or weak positive recombinant human transglutaminase (tTG)-specific IgA titer at Screening
OR
For a subject with selective IgA deficiency (~2% of celiac patients), deamidated gliadin peptide (DGP)-specific IgG titer is negative or weak positive at Screening.

6. If male subject, agrees to practice medically approved contraception that may include, but is not limited to, abstinence, monogamous relationship with a female who is not of child-bearing potential, surgical sterilization procedure (vasectomy), and or condoms throughout the study.

   If female subject, is not of child bearing potential (postmenopausal or premenopausal with surgical sterilization) or agrees to practice medically approved contraception that may include, but is not limited to, abstinence, monogamous relationship with a male who is post-surgical sterilization procedure (vasectomy), or agrees to use medically acceptable and highly effective birth control methods (e.g., an intrauterine device, a double-barrier method such as condom and spermicide or condom and diaphragm with spermicide, a contraceptive implant, injectable contraceptive, or oral contraceptive) throughout the study.
7. The subject is able and agrees to comply with study requirements.
8. The subject agrees not to participate in another interventional study while participating in the present study, defined as signing the informed consent form until completion of the last study visit.

4.2 Exclusion Criteria

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

1. The subject has a history of clinically confirmed immunoglobulin E (IgE)-mediated reaction and/or anaphylaxis to wheat (i.e., “wheat allergy”), barley or rye.
2. The subject has uncontrolled celiac disease and/or complications of celiac disease, or otherwise has experienced celiac symptomology within10 days of screening, in the opinion of the investigator.
3. The subject has a history of, or has an active, significant, clinically relevant, comorbidity (including Type 1 and Type 2 diabetes mellitus and other autoimmune disorders, splenectomy) that, in the opinion of the investigator, would make the subject unsuitable for participation in the study and/or could adversely affect interpretation of the study results.
4. The subject has had significant changes to or anticipates changes to prescription or non-prescription medication used to manage an underlying comorbidity within 30 days prior to Day 1.
5. The subject is currently taking or received systemic biologics 6 months prior to Day 1.
6. The subject has a compromised immune system, e.g.:

a. Known human immunodeficiency virus (HIV) infection or positive for HIV antibodies at Screening;

b. Subject is or has been taking immune suppressing medical treatment (e.g., azathioprine, methotrexate) during the 2 months prior to Day 1;

c. Subject is receiving immunosuppressive doses of corticosteroids (more than 20 mg of prednisone given daily for 2 weeks or more within 2 months prior to Day 1, any dose of corticosteroids within 30 days of Day 1, or high dose inhaled corticosteroids [>960 µg/day of beclomethasone dipropionate or equivalent]) within 30 days of Day 1.

7. The subject has a known history of hypersensitivity or allergies to TIMP-GLIA components or any other known severe hypersensitivity or allergic reaction (any reaction that resulted in hospitalization [initial or prolonged], congenital anomaly, or disability, or that required medical intervention to prevent permanent impairment or damage) to any other allergens (medications, food or environmental).
8. The subject has currently 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.
9. The subject has a history of any acute illness including, fever (>100.4°F or >38°C) within 14 days of Check In Day-1.
10. The subject has an active malignancy, or history of malignancy or chemotherapy within the past 5 years other than history of localized or surgical removal of focal basal cell skin cancer, cervical cancer in situ treated successfully in the past by local treatment (including but not limited to cryotherapy or laser therapy) or by hysterectomy.
11. The subject has known liver disease or serology positive for hepatitis C infection; positive hepatitis B surface antigen (HBsAg) at Screening Visit.
12. The subject has a positive test result for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, methylenedioxymethamphetamine), or alcohol in urine- except when positive result arises from treatment under a medical doctor's supervision - at Screening Visit or at Check-in.
13. The subject has a history of any drug or alcohol abuse in the past 5 years, or alcohol consumption greater than 21 units per week that, in the opinion of the investigator, would interfere with the subject's ability to comply with the study requirements. A unit of alcohol is equivalent to: 12 ounces of beer, 4 ounces of wine, or 1 ounce of spirits/hard liquor. Alcohol consumption will be prohibited 24 hours prior to entry into the clinical research unit until discharge.
14. The subject has the inability to undergo venipuncture or tolerate venous access as determined by the investigator or designee.
15. The subject has a history or presence of anorexia nervosa or other eating disorder.
16. If female, the subject is pregnant or lactating or intending to become pregnant before or during the study. The lack of pregnancy will be confirmed by serum assay for qualitative human chorionic gonadotropin at Screening and a urine assay performed at Check-in. Women with

postmenopausal status confirmed by screening follicle-stimulating hormone (FSH) result need not undergo subsequent urine pregnancy testing.

17. The subject has clinically significant laboratory results at Screening, as determined by the investigator, including, but not limited to the following:
    a. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) ≥ 1.5 times Upper Limit of Normal (ULN)
    b. Direct bilirubin outside the normal range
    c. Serum Creatinine > 1.2 mg/dL
    d. Hemoglobin < 10 g/dL
    e. Hematocrit < 30%
    f. Platelet count < 150,000 or > 400,000
    g. Serum Potassium, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), international normalized ratio (INR), or white blood cell count (WBC) outside the normal range (and judged clinically significant by the investigator)
18. The subject has clinically significant, abnormal electrocardiogram (EGC) at Screening, as determined by the investigator, including but not limited to:
    a. Mean QTcF interval >430 msec for males or >450 msec for females;
    b. ECG evidence of complete left bundle branch block (LBBB), right bundle branch block (RBBB) or incomplete LBBB;
    c. Mean intraventricular conduction delay with QRS duration >120 msec;
    d. Pathological Q-waves, defined as Q-wave >40 msec or depth >0.4 to 0.5 mV;
    e. Evidence of ventricular preexcitation.
19. The subject has received any investigational drug within 30 days or 5 half-lives prior to first dosing/Day 1.
20. The subject was previously enrolled and dosed in a clinical trial with TIMP-GLIA.
21. The subject received a live or inactive vaccine within 28 days prior or a subunit vaccine within 14 days prior to first dosing/Day 1 or the subject has a planned vaccination during the study.
22. The subject has donated blood or plasma ≤ 56 days prior to Screening and plans to donate blood or plasma within 5 weeks of completing the study.
23. The subject has received blood products, monoclonal antibody, or other systemic protein therapy within 6 months prior to first dosing/Day 1. NOTE: oral protein supplements are permitted.
24. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or may consent under duress.
25. The subject is unsuitable for enrollment in the opinion of the investigator for any other reason not specified above.

5 DISCONTINUATION

5.1 Discontinuation of Subjects

Subjects are free to withdraw consent for participating in the study at any time. Subjects will be informed that they are free to withdraw from the study drug treatment or study participation at any time and for any reason.

Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Possible reasons for subject discontinuation include the following categories:

Table 8. Categories of Subject Discontinuation

- Withdrawal of consent
- Occurrence of a pretreatment AE event that presented an unacceptable risk to the subject's health or the subject was unwilling to continue due to the AE, or occurrence of any other exclusion criteria prior to first dosing.
- Occurrence of a DLT or other serious or clinically significant AE that warranted discontinuation, in the opinion of the investigator.
- Major protocol deviation, including noncompliance with an inclusion or exclusion criterion, that is clinically relevant and affects subject safety or data integrity.
- Participation in a concurrent clinical study.
- Lost to follow-up.
- Study termination by Cour, the institutional review board (IRB) or FDA.
- Pregnancy.

5.1.1 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator in the source documentation and the primary reason for discontinuation by category (above) will be recorded in the electronic case report form ((e)CRF). Whenever possible, all subjects who withdraw from the study prematurely during the investigational period (through Day 60 visit) will undergo all final visit safety assessments (see SCHEDULES OF ASSESSMENTS

Table 1. Schedule of Procedures, Part A and Table 2. Schedule of Procedures, Part B).

Subjects who fail to return for study procedures during the investigational period will be contacted by the principal investigator or designee to seek compliance. A minimum of 2 documented phone calls should be made over the course of at least 2 weeks. If the study site personnel receive no response, and if the local government or regulatory agency permits, they should send a certified letter requesting that the subject contact the study site regarding his or her status in the study. The letter delivery certification should be retained in the source. Similar due diligence to obtain subject

status by telephone during the follow-up period and documentation thereof shall also be implemented.

5.1.2 Replacements of Withdrawn Subjects

Subjects who withdraw before receiving the first dose of study drug will be replaced. Subjects who withdraw after receiving study drug will be replaced at the sponsor's discretion. Replacement must occur to the same dose cohort.

5.2 Discontinuation of the Study

Although Cour has every intention of completing the study, it reserves the right to discontinue the study at any time for clinical or administrative reasons or if required by the FDA. The DMC will review the safety of TIMP-GLIA throughout the study. The occurrence of any medically important AE that could impact the safety of other subjects may lead to the discontinuation of the study after discussions between the medical monitor and Cour. The study will be terminated if the DMC determines that the Study Stopping Rules have been met.

5.3 Discontinuation of the Site

If the investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

6 STUDY TREATMENTS

6.1 Identity of Investigational Product

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 and approximate size distribution between ~200 nm and ~700 nm. There is ~10 µg of refined gliadin per mg of PLGA particles.

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.

TIMP-GLIA is to be reconstituted with 2.5 mL of Sterile Water for Injection (SWI), and further diluted for infusion with 0.9 % Sodium Chloride Injection, USP. The drug solution is to be administered by IV infusion using a controlled infusion device on the day of preparation. Specific reconstitution and dilution and storage instructions will be provided in the Pharmacy Manual.

6.2 Management of Clinical Supplies

6.2.1 Study Drug Packaging and Labeling

TIMP-GLIA will be manufactured, packaged, and labeled under the responsibility of qualified staff at Cour and/or Cour's designee(s) in accordance with the designee(s)'s standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines and applicable local laws and regulations.

Bulk vials will be provided to the study sites. 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, protocol number, lot number, expiry date or reevaluation date as applicable, and storage conditions.

TIMP-GLIA infusion solution will be prepared and labeled for individual subject dosing in the pharmacy of each clinical site. The IV bags containing study drug will bear a label conforming to regulatory guidelines including:

- Protocol number
- Subject identifier
- Drug and dose
- Date and time of preparation
- Date and time of expiration
- Caution statement: For Investigational Use Only

6.2.2 Storage and Handling

TIMP-GLIA vials should be stored at 2°C to 8°C (36° to 46° F) and protected from light in a secure, temperature-monitored, limited access location. All sponsor-supplied drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of each drug storage area must be maintained and temperature excursions documented. Detailed information on the storage conditions following reconstitution and dilution of study drug are provided in the Pharmacy Manual.

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (e.g. pharmacist), and

- that such deliveries are recorded;
- that study drug is handled and stored safely and properly in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs;
- that study drug is only dispensed to study subjects in accordance with the protocol;
- that any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

6.2.3 Inventory and Accountability

Study drug will be provided to the clinical site by Cour or its designee.

Drug inventory and accountability records for the study drugs will be kept by the investigator or designee (e.g., pharmacist).

The investigator or designee will acknowledge date of receipt and verify condition/quantities by signing the packing list/shipping form in the shipment. In addition, the date and time and quantity of study material prepared for/dispensed to each subject and by whom must be recorded on the drug accountability log. The required accountability for this study is vial count. Date/time vial is reconstituted and subject number should be written on the vial label to facilitate accountability. All used and unused containers are to be stored until accountability procedures are completed.

At the conclusion or termination of this study, the investigator or designee is to reconcile records of study drug delivery, preparation, dispensation, usage, and final disposition (destroyed or returned) to ensure completeness of the Drug Accountability Log and agreement with other clinical study records. Any discrepancies must be accounted for, including reasons for departure from the expected administration regimen and corresponding vial quantities. Appropriate forms and records must be signed by the person responsible.

Used or unused study drug may be destroyed at the study site according to standard institutional procedures after drug accountability has been conducted by the sponsor or representative, only if agreed upon by the sponsor. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request. Unused study drug not destroyed at the site must be returned to the sponsor or designee at the end of the study or upon expiration.

An institutional standard operating procedure for inventory and accountability may be implemented if reviewed and approved by the sponsor.

6.2.4 Ancillary Materials

Detailed information regarding necessary ancillary supplies (e.g., syringes, filters, infusion sets, IV bags) are provided in the Pharmacy Manual. Ancillary supplies may be provided by the sponsor or obtained by the clinical site from commercial sources.

6.3 Method of Assigning Subjects to Treatment Groups

Enrollment will occur competitively across initiated clinical sites. Prior to enrollment of an eligible subject, the investigator or designee is to request enrollment in writing to the sponsor's designee who will provide dose assignment and confirm subject identification (ID) number as appropriate and who will track subject enrollment/dose date/completion/discontinuation and screen failures. The designee will also coordinate dose scheduling such that dosing of individual subjects within a cohort (Part A and Part B) is compliant with protocol requirments.

Subjects meeting eligibility criteria who are enrolled in this study will receive open-label TIMP-GLIA.

The 9-digit subject ID number will be as follows:
3-digit country code-3-digit site number-3-digit sequential number

Once a subject ID number has been assigned to a subject it will not be reused for another subject. If a subject withdraws prematurely from the study and is replaced, a new subject ID number will be assigned to the replacement subject. The replacement subject will receive the same treatment as the person being replaced.

6.4 Blinding

Not applicable for this study.

7 TREATMENT ADMINISTRATION

7.1 Dose and Regimen

Aseptic technique must be used for the preparation and administration of TIMP-GLIA. Detailed instruction will be provided in the Pharmacy Manual.

TIMP-GLIA will be administered once as an IV infusion by a controlled infusion device. The planned doses will range as shown in **Error! Reference source not found.**. The dose to be investigated in Part B will be the maximum tolerable dose reached in Part A.

The lyophilized drug product will be reconstituted in the vial with SWI and then further diluted for infusion according to the Pharmacy Manual. The preparation of the dose will be confirmed by a second member of the study site staff.

Dosing will occur on Day 1 in Part A and on Day 1 and Day 8 in Part B (7 days apart). Subjects should remain supine during dosing.

As a safety precaution, venous access should be maintained for emergency use for 24 hours after dosing.

On dosing days, subjects will receive the assigned study drug after the subject has fasted from food and beverage approximately 2 hours prior to infusion start and 1 hour after infusion end. Water may be provided ad libidum.

For Part B, TIMP-GLIA should 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

7.2 Safety Committee (Dose Levels < 2 mg/kg)

A Safety Committee was convened to monitor the safety of subjects up to the 2 mg/kg dose cohort.. The Safety Committee included the: principal Investigator(s) (PIs) or PI(s)'s delegate(s) and a medical consultant with expertise in CD.

The role of the Safety Committee is described in prior versions of this protocol under which the 0.1 mg/kg, 0.5 mg/kg, and 1 mg/kg doses were administered.

7.3 Data Monitoring Committee (Dose Levels ≥ 2 mg/kg)

An independent DMC will be commissioned for this study for dose levels ≥ 2 mg/kg. The DMC will be comprised of 3 physicians with expertise in immunology and/or vaccines clinical trials. A 4th physcician with expertise in CD will serve as an advisor to the DMC, but in a non-voting capacity.

The sponsor medical monitor will not be a member of the DMC. The sponsor medical monitor and other study team members will be available to answer questions of the DMC as necessary and during Open Sessions of the DMC. The medical monitor and other study team members will not participate in Closed Sessions of the DMC. The DMC will convene when each dose cohort is completed to determine if it remains acceptable to continue dosing subjects. The DMC may also convene ad hoc to address emerging safety concerns. The DMC will evaluate the available safety data post-infusion, including but not limited to, AEs, vital signs, pulse oximetry, 12-lead ECGs and available laboratory results (e.g., hematology, chemistry, coagulation, and urinalysis, cytokines) in the context of the established Study Stopping Rules.

The following decisions may be made if stopping criteria are not met:

- Escalate the dose as planned
- Expand the dose cohort to 2 subjects (accelerated titration 2 + 2, Part A and Part B) or 6 subjects (standard 3+3, Part A)

  After a rate of DLTs has been identified for a specific dose in 3- or 6-subject cohorts, the DMC may recommend that up to a total of 12 subjects may be accrued at any dose level to better define the relationship between dose and emerging the safety signals.
- Decrease the dose either to a previous lower dose or to an intermediate dose
- Escalate the dose to an intermediate level if warranted based on events in the previous cohort

The decision(s) of the DMC to continue dosing will be documented and provided to the investigators prior to dosing any new subjects.

Additionally, the DMC may meet ad hoc to determine if it remains acceptable to continue dosing.

The medical monitor is to be notified of any serious adverse event (SAE) and any CTCAE Grade 2 or greater toxicity within 24 hours of investigator's (or designee's) awareness of such an event.

7.4 Progression or Termination of Dosing

Dosed subjects will remain under medical supervision in the clinic for 48 hours after dosing. Emerging safety data will be evaluated by the DMC against the Study Stopping Rules (Section 7.4.6) and defined dose limiting toxicity (Section 7.4.5).

7.4.1 Premature Termination of An Individual Subject's Infusion

If a subject develops signs and symptoms of IRR (dyspnea, generalized cutaneous reactions, tachypnea, hypoxia, tachycardia, or if the subject experiences a decrease in blood pressure the investigator should stop the infusion for a minimum of 5 minutes or until signs and symptoms subside. Depending upon the severity of the signs and symptoms, and at the investigator and subject discretion, the infusion may be restarted as follows:

- Restart the infusion at 25% of original rate for 15 minutes
- If subject tolerates the reduced rate, increase to 50% of original rate for another 15 minutes, then increase to the original rate until infusion is complete

Infusion will be permanently discontinued if the subject develops clinical signs and symptoms of Grade 3 or 4 IRR or anaphylaxis/ anaphylactoid reaction (any combination of nausea, vomiting, myalgia, rigors, fever [oral temperature ≥ 2°C above baseline]) and/or clinically significant dyspnea, generalized cutaneous reactions, tachypnea (doubling of baseline respiratory rate, resting), hypoxia (oxygen saturation < 90% on room air), tachycardia (resting heart rate > 120 bpm), or if the subject experiences a decrease in blood pressure that requires therapeutic intervention or other SAE, or if the subject experiences any other clinically significant AE which, in the opinion of the investigator, warrants termination of infusion.

7.4.2 Dosing Subjects Within A Dose Level (Within A Cohort)

Part A

During Part A (dose escalation), 1 subject will be dosed at a time followed by in-clinic observation for at least 48 hours. At least 168 hours (7 days) will elapse prior to dosing the next subject at the same level. This staggering is to provide sufficient time for acute adverse effects to emerge before additional subjects are exposed.

Dosing additional subjects in a cohort will be stopped if 1 of the subjects at a dose level exhibits a dose-limiting toxicity (DLT) or should any subjects in the current dose cohort or *any previously dosed subject (in any dose group)* develop clinical signs and symptoms of Grade 3 or 4 IRR or anaphylaxis/anaphylactoid reaction (any combination of nausea, vomiting, myalgia, rigors, fever [oral temperature ≥ 2°C above baseline]) and/or clinically significant dyspnea, generalized cutaneous reactions, tachypnea (doubling of baseline respiratory rate, resting), hypoxia (oxygen saturation < 90% on room air), tachycardia (resting heart rate > 120 bpm), or a decrease in blood pressure that requires therapeutic intervention or other SAE.

Dosing of additional subjects in a cohort will also be stopped upon the occurrence of 2 or more of the same CTCAE Grade 3 toxicity (among total subjects dosed) or the first occurrence of a CTCAE Grade 4 or Grade 5 toxicity, irrespective of relationship to study drug.

In this situation, the DMC will evaluate the cause of the abnormalities and whether they represent a drug-related safety concern, warrant implementation of additional safety precautions, dose groups, or other protocol changes, or justify study termination (i.e., Study Stopping Rules fulfilled).

If 1 of the subjects at a dose level exhibits dose-limiting toxicity and the DMC confirms the study will continue, an additional 2 subjects (accelerated titration 2+2, Part A) or 3 subjects (standard 3+3, Part A) will be dosed at the same level, staggered appropriately, so that a total of 4 subjects (accelerated titration 2+2) or 6 subjects (standard 3+3) will receive the same dose. (See **Error! Reference source not found.** .) After a rate of DLTs has been identified for a specific dose in 3- or 6-subject cohorts, the DMC may recommend that up to a total of 12 subjects may be accrued to better define the relationship between dose and emerging safety signals.

When all subjects in a dose level cohort complete procedures through 168 hours (7 days) post dose, the overall safety and tolerability data (AEs, vital signs, 12-lead ECGs, clinical laboratory tests, cytokines) and available cumulative AE data from previous cohorts will be reviewed by the DMC who will determine the progression or termination of dosing to the next dose level.

Part B

During Part B (repeat dose), subjects will receive 2 doses followed by in-clinic observation for at least 48 hours after each dose. At least 48 hours (2 days) will elapse after the second dose and safety confirmed before subjects in next higher dose cohort can be dosed. If dose-limiting toxicity occurs in 1 of the 2 subjects in Part B, the DMC may decide to increase enrollment at the same dose level by 2 subjects (n=4).

7.4.3 Dose Escalation – Dosing Subjects At the Next Dose Level

After all subjects at a dose level have completed study procedures through Day 8 (168 hours [7 days] post dose), the overall safety and tolerability of the dose will be determined by DMC evaluation of the safety data (AEs, vital signs, 12-lead ECGs, clinical laboratory tests) for the current cohort and available cumulative AE data from previous cohorts against the Study Stopping Rules.

The DMC will decide whether dose escalation and enrollment of the next dose group should occur.

If none of the subjects in the cohort experiences a DLT and stopping criteria are not met based upon DMC assessment of accumulating safety data, then escalation to the next higher dose may proceed.

If 2 or more subjects experience DLT(s) at a dose level, the prior dose level will be defined as the maximum tolerable dose (MTD) . The highest dose level that did not cause unacceptable side effects will be considered the MTD.

7.4.4 Dose Reduction

Depending upon emerging safety data, the DMC may recommend dosing a cohort of 2 subjects (accelerated titration 2 + 2, Part A and Part B) or 3 subjects (standard 3+3, Part A) at a dose lower than the planned level to better identify the maximum tolerable dose of TIMP-GLIA.

7.4.5 Dose Limiting Toxicity Definition

DLT is defined to be an AE or set of AEs that prevents further administration of the agent at that dose level. For this study DLT is defined as occurrence of:

- A CTCAE Version 4.0 Grade 3 or higher that is at least possibly related to TIMP-GLIA; or
- Suspected drug-induced liver injury (DILI) at least possibly related to TIMP-GLIA in any dosed subject indicated by
    - ALT or AST > 3x upper limit of normal (ULN) and increase of total bilirubin > 2x ULN without evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome ("Hy's Law") or
    - ALT or AST > 3x ULN and INR > 1.5x ULN or
    - ALT or AST >8xULN or
    - ALT or AST >5xULN for more than 2 weeks or

  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Any other toxicity which in the opinion of the DMC would not allow continued dosing if this were a repeat dose study

7.4.6 Study Stopping Rules

- First occurrence of a Grade 4 or Grade 5 toxicity at least possibly related to TIMP-GLIA
- 2 or more of the same Grade 3 toxicity considered to be at least possibly related to TIMP-GLIA (among total number of subjects dosed)
- 1 subject experiences a Grade 3 toxicity considered to be at least possibly related to TIMP-GLIA and in the same organ system another subject experience a Grade 2 or higher toxicity considered to be at least possibly related to TIMP-GLIA (at same dose level)
- Any other toxicity which in the opinion of the DMC would have precluded administration of a second dose if this were a multi-dose study

7.5 Treatment Compliance

The subject will be administered study drug in the clinical research unit by qualified staff. The date and infusion start and stop time and total volume infused are to be recorded. In the event of an interruption of an infusion, the stop/restart times of the interruption should also be documented as well as reason/circumstances. Compliance will be evaluated through review of study drug dispensing and administration records.

7.6 Emergency Procedures and Management of Overdose

In the event of adverse clinical responses to TIMP-GLIA infusion, interventions should be guided by the subject's symptoms and condition. Acute interventions for anaphylaxis/anaphylactoid reaction may include, but are not limited to, supplemental oxygen, endotracheal intubation and mechanical ventilatory support, supportive IV fluid administration, and/or Advance Cardiac Life Support (ACLS) therapies. If appropriate, transfer to an acute care hospital facility should be performed.

An overdose is defined as a known deliberate or accidental administration of TIMP-GLIA to a study subject at a dose above that which was assigned to the subject according to the study protocol.

There are no defined emergency procedures for an overdose of study drug. Treatment should be guided by symptoms.

All cases of overdose and any AE resulting from the overdose are to be documented in the source. Any case of overdose should be reported to the sponsor as a "special situation" (see protocol section 8.6.7 Collection and Reporting of Special Situations). Serious AEs arising from overdose are to be reported accordingly (see 8.6.2 Serious Adverse Events and 8.6.6 Collection and Reporting of Serious Adverse Events).

7.7 Restrictions During the Study/Treatment Conditions

Subject habits will be assessed at screening for study eligibility. Compliance with study restrictions with respect to eligibility criteria is to be confirmed at Day 1/prior to first dosing and thereafter compliance with study restrictions are to be assessed at each visit, including telephone "visits".

7.7.1 Clinic Residency and Clinic Visits

Subjects participating in Parts A and B will report to the clinical research unit one day (Day-1) before the first dose and will remain residential in the clinic until completion of study procedures on Day 3. If, in the opinion of the investigator, a subject's condition warrants longer medical observation, clinic discharge may be delayed. Subjects participating in Part B will return for clinic admission one day (Day 7) prior to the second dose and will remain residential until completion of study procedures on Day 10. Clinic discharge may be delayed if extended medical observation is indicated.

All subjects will report to the clinic for scheduled outpatient visits, which are indicated in the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2). Unscheduled clinic visits to follow up suspected AEs or to permit sample collection may also be arranged at the discretion of the investigator. If necessary arrangements can be made, visits to remote sample collection laboratories to permit sample collection may be allowed, if necessary to avoid missed procedures or to facilitate AE follow-up, with prior discussion between the sponsor and investigator.

Follow up via telephone contact is to be arranged according to the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2) and as needed by the subject or clinic staff to ensure safety, data completeness, and logistics for future study activities.

7.7.2 Dietary and Fluid Restrictions

Consumption of alcohol will be prohibited from 24 hours prior to clinic admission until discharge from the clinic. To avoid false-positive results from the drug screen, food and drinks containing poppy seeds will not be allowed during the study. To facilitate compliance subjects should be reminded that testing for the presence of drugs of abuse and alcohol will be performed at Screening and each clinic admission (check-in).

Standardized gluten-free meals (breakfast, lunch, dinner) and non-alcoholic beverages will be served at consistent times relative to dosing and performance of study procedures while subjects are confined in the clinic. Meals must not interfere with any study procedures. The menu and nutritional information is to be archived in the study file.

When not confined, subjects are to maintain a GFD from the time of screening through the final study procedure.

7.7.3 Exercise

Subjects are to refrain from strenuous exercise from screening through the last study procedure/Late Follow-up Visit. Subjects should be encouraged to walk and stretch while in clinic to avoid AEs associated with the sedentary environment.

7.7.4 Use of Tobacco- or Nicotine-Containing Products

Subjects are not allowed to smoke or use tobacco- or nicotine-containing products during clinic residency.

8 EVALUATIONS AND ASSESSMENTS

8.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be collected at Screening. This will include sex, race, ethnicity, and date of birth, height, weight, and calculated BMI. Weight may be recorded at additional timepoints.

Height (m) and weight (kg) are to be recorded while the subject is wearing indoor clothing with shoes off. Body mass index (BMI) will be calculated as weight (kg)/ height $(m)^2$.

8.2 Medical History, and Medication History

A complete medical history, medication history and history of smoking/tobacco and alcohol habits will be recorded at Screening and reviewed for any changes at clinic check in (Day 1) to ensure compliance with the study eligibility criteria.

The medication history includes use of any prescribed or nonprescription medications, medications given as part of any surgical procedure, and dietary supplements (including vitamins, minerals, natural and herbal remedies) taken at least once in the 6 months before Screening.

The medical history should include clinically significant medical or surgical history ongoing at baseline or with onset in the previous 2 years. Subjects will be asked about previous diseases and conditions to allow thorough evaluation of the study eligibility criteria. Medical history assessment will include but is not limited to questions about gastrointestinal disease, malignancies, diseases associated with immunosuppression, allergies and hypersensitivity reactions, hepatitis, HIV, and infectious diseases requiring systemic treatment within the last 2 weeks and about any participation in other clinical trials.

8.3 Diet History (Subjects With Celiac Disease)

A dietary history will be obtained from each subject via interview/questionnaire and adherence to a GFD is to be confirmed at Screening. Because the CD serology titers (tTG, DGP) are likely to be positive if subjects have not been following a GFD for at least 6 months or if they have recently (within at least 10 days) experienced gluten exposure, the outcome of the diet history discussion may prevent unnecessary blood tests. Performance of the CD serology may proceed at the discretion of the investigator if diet history is not completely known and there is a reasonable possibility for negative or weak positive titers.

8.4 Concomitant Medications

All concomitant medications from the time of the first study drug dose through the last study visit will be recorded. Medication used prior to first dosing will be recorded as medication history as in Section 8.2 Medical History, and Medication History).

Concomitant medication includes all medicinal products other than TIMP-GLIA including prescribed or nonprescription medications, medications given as part of any surgical procedure, and dietary supplements (including vitamins, minerals, natural and herbal remedies). If a subject

discloses participation in another interventional clinical trial during the course of the current study, the investigational product administered to the subject will be recorded as a concomitant medication.

Subjects must be instructed not to take any medications, including over-the-counter medications, without first consulting with the investigator. Only stable medication to manage underlying comorbidity, stable hormone replacement therapy, or contraceptives identified at Screening and approved by the investigator and sponsor may continue during the study. Occasional use of acetaminophen (no more than 2 g/day) may be allowed but non-medication treatment such as a cold compress should be tried before over-the-counter analgesic use.

Any concomitant medications deemed necessary for the management of an AE during the study may be given at the discretion of the investigator. It is the responsibility of the investigator to ensure that the details regarding the medication are recorded in full (e.g., product name [with description if necessary], dose/quantity, method of administration, frequency, usage start/stop date, usage start/stop time if applicable, reason). Usage of any concomitant medication other than acetaminophen may result in withdrawal of the subject unless, after discussion between the investigator and sponsor's medical monitor, it is concluded that the medication is not expected to influence the outcome of the study.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHO Drug).

8.5 Safety Assessment

8.5.1 Physical Examination

Physical examination will be performed according to the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2).

A full physical examination (PE) will consist of an assessment of general appearance; eyes; ears, nose, throat; cardiovascular system; chest (lungs)/respiratory system; abdomen (liver, spleen); skin; extremities; musculoskeletal system; neurological system, including mental status; neck/thyroid/lymph nodes; and other. The abbreviated PE will include assessment of general appearance; skin; chest (lungs)/respiratory system; cardiovascular system; abdomen (liver, spleen).

Any abnormal finding observed during the screening visit must be assessed and documented as not clinically significant (NCS) if a subject is to be enrolled in the clinical study. After study drug administration, new abnormal findings or a worsening of an ongoing abnormal condition will be recorded as an AE.

8.5.2 Vital Sign Measurements

Vital signs will be measured every 15 minutes during the infusion and as otherwise specified in the *Schedules of Procedures* for Part A (Table 1) and Part B (Table 2).

Body temperature will be an oral or tympanic measurement and methodology documented. Systolic blood pressure and diastolic blood pressure (SBP and DBP) and pulse (beats per minute) will be measured using a semiautomatic blood pressure recording device with an appropriate cuff size. Blood pressure and pulse will be measured after the subject has rested for at least 5 minutes in the supine position. Respirations will be counted and documented in breaths per minute. Additional vital sign measurements may be performed as needed at the investigator's discretion.

8.5.3 Pulse Oximetry

Oxygen saturation will be continuously monitored via pulse oximetry with a fingertip monitor, predose through 4 hours postdose. Values should be recorded at the timepoints specified in the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2).

Additional timepoints should also be recorded if necessary, at the discretion of the investigator, to follow up suspected adverse events.

8.5.4 Routine Electrocardiogram for Safety

Routine ECG measurements will be performed according to the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2) after the subject has been in a supine position for at least 5 minutes. Routine ECG measurements will be performed in triplicate at Screening visit and on Day -1 (predrug baseline). Triplicate ECGs will be performed with a 1 minute interval and all 3 ECGs completed within 5 minutes. At all other time points, routine ECG measurements will be performed as a single measurement.

The investigator will review, sign and date the ECG after recording to ensure the subject's safety. The time of the ECG, as well as an overall conclusion, will be documented within the source. The investigator will interpret the ECG using 1 of the following categories: normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). If the overall conclusion is abnormal CS, the applicable AE must be recorded within the source.

The ECG tracings should be collected and retained with the source documents for study monitoring.

If possible the electronic data file with all generated ECG variables and electronic files with the digitized tracings will be transferred to the sponsor at the end of the clinical study.

8.5.5 Real-time Cardiac Monitoring (Electrocardiogram Telemetry)

Real-time cardiac monitoring will be performed as depicted in the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2) as a tool to facilitate medical management of the subjects after dosing. The telemetry results will be reviewed by the investigator on a regular basis to identify

potential abnormalities. Start and end date and time of the telemetry will be documented within the source and any findings will be appropriately characterized (normal, abnormal NCS or abnormal CS). If telemetry findings are evaluated as abnormal CS, the appropriate AE should be documented within the source.

8.5.6 Laboratory Assessments

Samples for standard clinical laboratory tests will be obtained according to the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2). Laboratory tests to be performed in this study are shown in Table 9. Clinical Laboratory Tests.

Blood samples will be collected via a peripherally placed IV cannula or by direct venipuncture in a suitable forearm vein. Samples for clinical chemistry will be collected under fasting conditions and in accordance with acceptable laboratory procedures/protocols.

A "clean catch" method will be used for urine collections.

Non-standard laboratory tests will be performed by appropriate bioanalytical laboratories specified by the sponsor. Details for collection, processing, storage (if applicable), and shipment are provided in the Laboratory Manual.

8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety

Standard laboratory tests for screening/safety will be performed by each site's local laboratory. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening value is noted, the clinically significant value and reason for clinical significance will be documented as an AE (as described in Section 8.6.1). The investigator will continue to monitor the subject with additional assessments until the values have reached reference range or the values at Screening, or until the investigator determines that follow-up is no longer medically necessary.

Results should be reported immediately to the investigator and transferred electronically at the end of the study for incorporation into the trial database. Test data transfers should be performed to check accuracy and completeness.

- Standard hematology, serum chemistry, coagulation, and urinalysis.
- A 24-hour urine collection for protein and creatinine measurement may be ordered at the investigator's discretion to follow up an abnormal urine-protein-to-creatinine ratio (UPCR) indicating protein in the urine.

- Urine testing for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates) and alcohol. (Breathalyzer testing for presence of alcohol may also be used at clinic check in place of the urine test.)
- A serum pregnancy test (qualitative human chorionic gonadotropin [hCG]) is required at screening. A urine pregnancy test may be performed at each clinic check in.
- A follicle-stimulating hormone (FSH) test may be performed at screening to confirm menopausal status. Women with postmenopausal status confirmed by screening FSH result need not undergo subsequent urine pregnancy testing.
- Serology for hepatitis and HIV

Table 9. Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation	Urinalysis

Red blood cells (RBC) Reticulocytes (Retic) Hemoglobin (HGB) Hematocrit (Hct) Mean corpuscular volume (MCV) Platelets (PLT) White blood cells (WBC) WBC differential (absolute, relative %) Neutrophils (Neutro) Monocytes (Mono) Eosinophils (Eos) Basophils (Baso) Lymphocytes (Lymph)	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bilirubin, indirect Bilirubin, total (TBL) Blood urea nitrogen (BUN) ***BUN/creatinine ratio*** Calcium (Ca) Carbon dioxide (CO_2) or Bicarbonate Chloride (Cl) Cholesterol (total) Creatinine (Cr) Creatine kinase (CK) Glucose γ-Glutamyl transferase (GGT) Globulin ***Calculated Albumin/globulin ratio*** Lactate dehydrogenase (LDH) Magnesium Phosphorus/Inorganic phosphate Potassium Sodium Triglycerides Total protein Uric acid ***Calculated creatinine clearance*** Human chorionic gonadotropin (hCG) Follicle-stimulating hormone (FSH) if menopause is suspected	Prothrombin time (PT) Partial Thromboplastin Time (PTT) International Normalized Ratio (INR) <u>Additional thrombotic/vascular markers (a)</u> D-dimer vWF ICAM-1 Fibrinogen Prothrombin Fragment 1,2 P-selectin	<u>Dipstick</u> Bilirubin Blood Glucose Ketones Leukocytes Nitrate (Nitrite) Protein Urobilinogen pH Color Specific gravity Turbidity ***Urinary protein to creatinine ratio (UPCR)*** (by random [spot] direct measurement) <u>Microscopy (if abnormalities observed on parameters above)</u> Casts Crystals Epithelial cells Leucocytes Erythrocytes Bacteria
Hepatitis & HIV Serology	Anti-Drug and CD-Related Serology	Additional Tests	Drugs of Abuse and Urine Pregnancy
Hepatitis B surface antigen (HBsAg) Hepatitis C virus antibodies (Anti-HCV) Human immunodeficiency virus (types 1 and 2) HIV-1 and 2 antibodies	Anti-gliadin antibody (i.e., Anti-drug antibody as deamidated gliadin peptide [DGP]-specific IgG antibody) Total serum Immunoglobulin A (IgA) (total IgG and IgM may be obtained when necessary to clarify results of IgA test) <u>"Celiac Serology" Tests</u> Tissue transglutaminase (tTG)-specific IgA antibody Deamidated gliadin peptide (DGP)-specific IgG antibody	<u>Serum-Anaphylaxis/anaphylactoid reaction</u> Acute phase cytokines multiplex cytokine panel(s): EGF, fractalkine, GM-CSF, GRO α, IFNα, IFN-γ, IL-1α, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, MIP1α, and MIP1β, TNF-α (b) <u>Mast cell activation</u> Tryptase (a) <u>Additional Complement markers</u> C3a, C5a, CH50, SC5B-9 (a, d)	<u>Urine</u> Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Opiates <u>Breath/Blood/Urine</u> Alcohol <u>Urine Pregnancy</u> Human chorionic gonadotropin (hCG)

Table 9. Clinical Laboratory Tests, continued

Hepatitis & HIV Serology	Anti-Drug and CD-Related Serology	Additional Tests	Drugs of Abuse
		Whole blood /isolated PBMCs Phenotyping for HLA-DQ2.5 (HLA-DQA1*0501 / B1*0201) and HLA-DQ8.1 (DQA1*0301/B1*0302) T-cell proliferation and cytokine secretion in response to ex vivo gliadin stimulation (a) (c) Immune Complex Detection C1q binding	

Abbreviations defined in Section V, List of Abbreviations.

See protocol text regarding timing of sample analysis.

a) Collect sample Predose but post dose if /when clinically indicated (prn) upon appearance of symptoms of anaphylaxis/anaphylactoid reaction or IRR (such as fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea).
See protocol text regarding timing of sample analysis.

b) Collect sample Predose and at scheduled post-dose timepoints (see Table 1. Schedule of Procedures, Part A or Table 2. Schedule of Procedures, Part B) but additional times post dose if/when clinically indicated (prn) upon appearance of systemic symptoms of anaphylaxis/anaphylactoid reaction/cytokine release syndrome or IRR such as fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea.
See protocol text regarding timing of sample analysis.

c) Post-dose blood samples will be collected at approximately 144 hoursfor the single dose groups ≥ 4 mg/kg in Part A and on Days 8 (pre-dose) and 14 for the repeat dose group in Part B, for measurement of peripheral blood T cell proliferation and cytokine secretion in response to ex vivo gliadin stimulation.

d) For Part B, collect sample for C3a, C5a, and SC5B-9 complement levels at 15 and 30 minutes during infusion and at 24 hours following infusion.

8.5.6.2 Celiac Genetics

Phenotyping for HLA-DQ2.5 (HLA-DQA1*0501 / B1*0201) and HLA-DQ8.1 (DQA1*0301/B1*0302) will be performed by a bioanalytical laboratory specified by the sponsor. Blood sampling, processing, and shipment instructions are provided in the laboratory manual.

8.5.6.3 Celiac-Related Serology

Total serum Immunoglobulin A (IgA), tissue transglutaminase (tTG)-specific IgA antibody or deamidated gliadin peptide (DGP)-specific IgG antibody will be measured at a bioanalytical laboratory specified by the sponsor. Instructions for blood sampling, processing, and shipment are provided in the laboratory manual.

8.5.6.4 Immunogenicity (Anti-Gliadin Antibodies) and Immune Complex Formation

Measurement of anti-gliadin antibodies (i.e., anti-drug antibodies) and immune complex detection by C1q binding in serum will be performed using validated methodology at a bioanalytical laboratory(ies) specified by the sponsor. Specifically, deamidated gliadin peptide (DGP)-specific IgG antibody will be used as the anti-drug antibody test.

Blood sampling, processing, storage, and shipment instructions are provided in the Laboratory Manual.

8.5.6.5 C3a and SC5B-9 Complement Levels

For Part B, C3a and SC5B-9 complement levels will be obtained during the infusion and 24 hours following the infusion (refer to Table 2. Schedule of Procedures, Part B).

8.5.6.6 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction

These tests will be performed by a bioanalytical laboratory specified by the sponsor, with instructions for blood sampling, processing, storage (if applicable), and shipment provided in the Laboratory Manual. Performance of testing (relative to collection or processing time) should be compliant with sample stability limits and validated procedure requirements, as applicable.

8.5.6.6.1 Cytokines

Samples for determination of acute phase cytokines (EGF, fractalkine, GM-CSF, GRO α, IFNα, IFN-γ, IL-1α, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, , IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, MIP1α, and MIP1β, TNF-α,) are to be collected predose and at scheduled post dose timepoints (for all subjects). (See Table 1. Schedule of Procedures, Part A and Table 2. Schedule of Procedures, Part B.) Additional samples are to be obtained as needed from subjects exhibiting systemic symptoms of anaphylaxis/anaphylactoid reaction/cytokine release syndrome or IRR such as fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea.

The IFN-γ, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, and TNF-α results through 24 hours post dose will be used for dose escalation decision. In the event of the appearance of clinical symptoms, this acute phase cytokine testing should be performed promptly and results are to be reported to the investigator as soon as possible.

The scheduled predose and post dose samples can be batched and tested for the other cytokines at the end of the trial unless otherwise specified by the medical monitor, sponsor, or DMC or as necessary for compliance with the established sample stability.

8.5.6.6.2 Mast Cell Activation and Complement Activation and Supplementary Vascular/Thrombotic Assessment

Symptoms of anaphylaxis/anaphylactoid response or IRR (e.g., fever, nausea, chills, rigors, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, and dyspnea) will be followed up with additional laboratory testing for mast cell activation (Tryptase), complement activation (C3a, C5a, CH50, SC5B-9), and for vascular/thrombotic markers (D-dimer, vWF, ICAM-1, Fibrinogen, Prothrombin Fragment 1,2 and P-selectin).

Predose samples will be obtained from all subjects, with additional post dose samples to be taken from symptomatic subjects prn if clinically indicated by the appearance of symptoms.

Samples should be analyzed promptly and results are to be reported to the investigator as soon as possible in the event of clinical presentation of anaphylaxis/anaphylactoid response or IRR.

If clinical symptoms did not arise the (predose) samples will not be analyzed unless otherwise specified by the sponsor, medical monitor, or DMC or as necessary for compliance with the established sample stability (e.g., if predose sample must be analyzed to prevent sample expiration prior to end of trial).

8.5.6.6.3 Whole Blood for PBMC Isolation

Samples will be obtained from all subjects predose. Additional post dose sample(s) will be collected prn if clinically indicated by the appearance of symptoms of anaphylaxis/anaphylactoid response/cytokine release syndrome or IRR. Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood samples. PBMCs will be used to determine T cell proliferation and cytokine secretion in response to ex vivo gliadin stimulation (by an established proliferation assay). Surplus PBMCs, if any, might be used to perform the alternative assay.

Scheduled post-dose blood samples will be collected at approximately 144 hoursfor dose groups ≥ 4 mg/kg in Part A and on Days 8 (predose) and 14 for the repeat dose group in Part B.

8.6 Adverse Events

AEs will be collected from time of consent until final follow up. The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with study participation or study treatment. AEs that occur after a subject provides informed consent but before the time of the first dose of study drug will be considered pretreatment AEs.

8.6.1 Treatment Emergent Adverse Events

A treatment emergent adverse event (TEAE) is defined as any untoward medical occurrence in a clinical investigation subject administered study drug; it does not necessarily have a causal relationship with study drug. *For simplicity, the protocol will refer to AEs. The distinction of TEAE will be made in the data by a subject's exposure to at least one dose of study drug.*

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

The following should not be recorded as AE:

- Preplanned procedures unless the condition for which the procedure was planned has worsened after the subject signed informed consent; (however, complications resulting from an elective surgery should be reported as AEs).

- Preexisting conditions found as a result of screening procedures. These should be recorded as medical history; (however, worsening of an ongoing abnormal preexisting condition is to be recorded as an AE).

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy or further diagnosis beyond repeat testing for confirmation alone. See also CTCAE Version 4.0 (Published: May 28, 2009 [v4.03: June 14, 2010]) or most current version.

Refer to Appendix 13.1, Liver Safety Monitoring and Assessment (Drug Induced Liver Injuiry, DILI) for detailed information on identifying, monitoring and assessing liver abnormalities if increases in liver function test values occur or a TEAE is suspected to be due to hepatic dysfunction.

8.6.2 Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Leads to a congenital anomaly/birth defect
- Is an important medical event:
  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 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 or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Any potential "Hy's Law" or severe hepatic function abnormality as defined below, in the absence of another etiology, is to be considered an important medical event and must be promptly reported as an unexpected SAE associated with the use of the drug (i.e., reported even before all other possible causes of liver injury have been excluded). (See also Appendix 13.1.)
    - ALT or AST > 3x upper limit of normal (ULN) and increase of total bilirubin > 2x ULN without evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome ("Hy's Law") or

- ALT or AST > 3x ULN and INR > 1.5x ULN or
- ALT or AST >8xULN or
- ALT or AST >5xULN for more than 2 weeks or
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The initial report must occur before fully working up the patient to rule out other etiologies. Reporting should include all available information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.6.3 AE Severity Assessment

The CTCAE Version 4.0 (Published: May 28, 2009 [v4.03: June 14, 2010]) or most current version will be used to assess and grade severity for AEs and laboratory abnormalities judged to be clinically significant. Within each category, AEs are listed accompanied by their descriptions of severity (Grade 1-5). Each AE term will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) term and code. For this study, the CTCAE will only be used for grading the severity for the AE and not for causality assessment.

If an event is not covered by CTCAE Version 4.0, the guidelines shown in Table 10 should be used to assess severity.

Table 10. Severity Criteria Descriptions for AE not covered by CTCAE

Toxicity Grade	Severity	Description
Grade 1	Mild	The event is transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom, but tolerates it reasonably well.
Grade 2	Moderate	The event causes mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Grade 3	Severe	The event causes marked limitation in activity, medical intervention/therapy required. Hospitalization possible.
Grade 4	Life-threatening	The subject is at risk of death due to the AE as it occurred. This does not refer to an event that hypothetically might have caused death if it was more severe.
Grade 5	Fatal	The subject dies due to the event.

8.6.4 Causality of AEs

The relationship of each AE to study medication(s) will be assessed by the investigator or delegated doctor of medicine (MD) subinvestigator using the following categories. If a licensed

physician assistant who is delegated responsibility by the investigator provides initial assessment of causality, it must be confirmed in writing by the investigator or MD subinvestigator.

Causal relationship to the study drug	Criteria for causal relationship
Not related	A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable temporal sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable temporal sequence to administration of the study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).

8.6.5 Documenting AEs

AEs should be recorded as descriptively as possible (investigator terms) in the source. Time of AE onset and resolution (if applicable) should be recorded for AEs occurring while the subjects are in the clinic. Source should be sufficiently detailed to allow appropriate medical evaluation of AEs and the circumstance under which they occurred and to facilitate accurate and efficient coding and eCRF reporting and determine the necessity of medical follow up.

At every study visit or telephone follow up, subjects will be asked a nondirected question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and non-prescribed/over-the-counter medications).

AEs must be followed to satisfactory resolution or until the investigator deems the event to be chronic or the condition to be stable. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness, etiology, and the likelihood of relationship of the AE to study drug.

Collection of pretreatment AEs will commence from the time the subjects signs the informed consent to participate in the study and continue until the subject is first administered study drug. For subjects who discontinue study participation prior to study drug administration, pretreatment events are collected until the subject discontinues. Collection of TEAEs will begin from the time that the subject is first administered study drug through the last study procedure.

Assessment of relationship to study drug will only be captured for TEAEs (AEs arising after the subject is first administered study drug). For AEs prior to dosing relationship to AEs will be deemed “not related”.

8.6.6 Collection and Reporting of Serious Adverse Events

The investigator may consult with the Cour medical monitor at any time regarding an AE; however, the Cour medical monitor is to be notified of any serious adverse event (SAE) and any Grade 2 or greater toxicity or DILI case within 24 hours of investigator's (or designee's) awareness of such an event.

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

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug
- Causality assessment.

The SAE form should be transmitted byfax within 24 hours of awareness to the attention of the contact listed below:

Attn: Drug Safety Coordinator
US Fax: +1 888-301-7843

The AE eCRF and other relevant eCRFs (such as General Medical and Surgical History, Prior/Concomitant Medications, Vital Signs, and Concomitant Procedures) for the subject must be completed promptly and updated promptly with new information. If there are additional documents that support the SAE (e.g., clinic or hospital records, laboratory reports, or procedure reports), they should be obtained. Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study drug. SAEs spontaneously reported >30 days after the last subject's last procedure will not be captured in the trial database.

8.6.7 Collection and Reporting of Special Situations

Some events will be considered "special situations" and reported using the SAE form (special situation section) even though an associated SAE may not have been experienced by the study subject. Examples are pregnancy (of a study subject or female partner of a male study subject; see also Section 8.6.9), overdose (see also Section 7.6), and medication error (i.e., an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient). Other "special situations" may be identified case-by-case.

8.6.8 Follow-up of SAEs

All SAEs should be followed up until resolution or until the investigator deems the event to be chronic or stable. The timelines and procedure for follow-up reports are the same as those for the initial report.

8.6.9 Pregnancy

Women with known or suspected pregnancy are excluded from the study.

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 30 days from the last procedure or last dose, whatever is greater, the subject should inform the investigator immediately and subsequently the investigator should report the information to the sponsor on the SAE form (special situation section) as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information. Should the partner of the male subject become pregnant, a separate informed consent form will be submitted for IRB review and approval that, upon signing by the pregnant female (subject's partner), will allow medical supervision during the pregnancy and allow follow-up after the birth of the infant.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including congenital anomaly or developmental delay in the fetus or the child]), the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, the death should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth (e.g., the Apgar score).
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination.

8.7 TIMP-GLIA Concentration and Pharmacokinetics

8.7.1 Blood Collection for PK

Serial blood samples will be collected in a K2 EDTA tube for measurement of TIMP-GLIA in plasma at the times relative to **infusion start time** as shown in the *Schedules of Procedures* for Part A (SCHEDULES OF ASSESSMENTS

Table 1) and Part B (Table 2). The scheduled times relative to infusion start should be implemented as indicated; however, some time windows of PK blood collection will be allowed, if necessary, as shown in Appendix 13.3.

Samples for PK are to be drawn from the opposite arm from which study drug is being infused.

Sample processing, storage, and shipment instructions are described in the Laboratory Manual. TIMP-GLIA concentration measurement will be performed by a validated ELISA assay (LLOQ = 0.05 µg/mL) by a bioanalytical laboratory specified by the sponsor. The method detects gliadin that has been released from the TIMP-GLIA matrix and is present in plasma.

8.7.2 Estimation of PK Parameters

Individual subject plasma TIMP-GLIA concentrations over time (*actual time elapsed from dosing*) will be used to derive PK parameters using non-compartmental analysis (NCA). The primary PK parameters are maximal observed concentration (C_{max}), last measurable concentration (C_{last}), time of maximal observed concentration (T_{max}), time of last measurable concentration (T_{last}), and area under the curve from time zero and extrapolated to infinity (AUC_{inf}) and area under the concentration-time curve from time zero to time of the last measurable concentration (AUC_{last}). Other PK variables will be derived if feasible: terminal elimination half-life ($t_{½}$), area under the curve over the dosing interval (AUC_{τ}), area under the curve from time zero (time of dosing) to time *t*, where a relevant *t* will be determined based upon the observed data (AUC_t), total body clearance (CL), volume of distribution (V_d), and accumulation index (R_{acc}). The terminal half-life will be calculated as $t½ = \ln(2)/\lambda_z$, where λ_z is the terminal rate constant. λ_z will be estimated as the slope from a linear regression with the natural logarithm to the concentration as the response variable, and time as the explanatory variable. Valid observations from the final part of the curve, which is approximately linear, will be used for the analysis. Pharmacokinetic analysis results may be provided in a separate PK report.

8.8 Total Amount of Blood

The approximate total blood volume taken per CD subject in Part A is 307mL and in Part B is 462 mL over 3 months (screening through Day 60). Volumes may increase should the subject require unscheduled testing to follow up suspected adverse events.

8.9 Priority of Actions

The following order of procedures will be in effect when more than 1 assessment is required at a time point with blood sampling for pharmacokinetics/metabolic profiling being collected nearest to the scheduled time point:

1. Routine 12-lead ECG
2. Supine vital signs
3. Dosing
4. Blood sample for PK collected at the nominal time point relative to dose (infusion START) time
5. Blood sampling for screening/safety and specialty laboratory tests
6. Urine sampling for safety laboratory tests

9 STATISTICAL METHODS

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock, at the latest. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives along with specifications for tables, listings and figures (TLFs) to be produced. Any changes from the analyses planned in the SAP will be justified in the clinical study report.

Prior to database lock a review of the clinical study data will be performed and final data queries identified, if necessary.

9.1 Sample Size

No sample size calculation was performed. The sample size is based upon precedent set by other clinical studies of similar nature and is considered sufficient to achieve the study objectives.

9.2 Analysis Sets

9.2.1 Safety Set

The safety analysis set (SAF) will include all enrolled subjects who received at least 1 dose of study drug.

The SAF will be used for summaries of demographics and baseline characteristics and all safety and tolerability variables.

9.2.2 Pharmacokinetic Analysis Set

The PK analysis set (PKAS) is a subset of the SAF for which concentration data are available to facilitate derivation of at least 1 primary PK parameter and for whom the time of dosing on the day of sampling is known. Inclusion of subjects in the PKAS with missing data or protocol deviations will be considered by the pharmacokineticist on a case-by-case basis.

The PKAS will be used for all tables and graphical summaries of PK data.

9.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics including sex, age, race, ethnicity, height, weight, and the HLA type (HLA-DQ2.5 or HLA-DQ8.1) will be summarized for the SAF and PKAS.

Medical history data will be summarized for the SAF using the number of observations and percentage of subjects reporting each category.

9.4 Subject Disposition

The number of subjects who enter and complete each phase of the study will be tabulated. Numbers of subjects who fail to complete the study will be tabulated and categorized by reason for termination.

All screen failures and corresponding primary reason for screen failure will be listed.

9.5 Safety Analysis

No formal statistical analyses will be conducted. All safety and tolerability data for the SAF will be listed. In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], minimum, median, and maximum and geometric mean where applicable) for continuous endpoints, and frequency and percentage for categorical endpoints. Percentages by categories will be based on the number of subjects with no missing data, i.e., will add up to 100%. Changes from predose baseline may also be presented for laboratory values, pulse oximetry, and vital signs as appropriate. Physical examination findings and ECG abnormalities will be listed.

Data will be presented overall and by dose level for each phase of study (Part A, Part B). Presentation by dose (mg) administered may also be included, as appropriate.

9.5.1 Adverse Events

AEs will be coded using MedDRA. All AEs will be listed.

AE summary tabulations will specify number and percentage of subjects who experienced an AE presented by MedDRA System Organ Class and MedDRA Preferred Term, and CTCAE grading (severity) overall and by dose level for each study phase (Part A, Part B). Separate summaries will be presented for TEAEs, serious TEAEs, TEAEs leading to discontinuation, and TEAEs related to study drug. The number of events will also be presented by MedDRA System Organ Class and MedDRA Preferred Term, and CTCAE grading (severity) overall and by dose level for each study phase (Part A, Part B). AE tabulation and listing descriptions will be provided in the SAP.

At each level of incidence reporting, a subject will be counted once if the subject reports 1 or more events at that level.

In the case of duplicate preferred terms for a subject:

- the most severe case will be reported
- drug relatedness status, most conservative assessment, will be reported

Additional AE data capture and reporting conventions include but are not limited to:

- If the *onset time* of an AE starting on Day 1 is not known relative to dosing start time on Day 1, the AE will be considered treatment-emergent.
- If only a partial AE *onset date* is available (month/year) and it is the same as the month/year of Day 1 and the full AE *end date* (day/month/year) is *on or after Day 1*, the AE will be considered treatment-emergent.
- If only a partial AE *onset date* is available (month/year) and the full AE *end date* is before Day 1, the AE will not be considered treatment-emergent.
- If only a partial AE *onset date* (month/year) and only a partial AE *end date* (month/year) are available and both are the same month/year of Day 1, the AE will be considered

treatment-emergent unless documentation specifies the *onset date and time* was prior to Day 1 dosing.

9.5.2 Vital Sign Measurements and Pulse Oximetry

Vital sign measurements (systolic and diastolic blood pressure [mmHg], heart rate [beats/minute], respiration rate [breaths/minute], and body temperature [°C]) and oxygen saturation (SO_2, %) measurements will be displayed in the listings and will be summarized in tabulations. In addition to summary statistics, inner quartile percentiles will be reported. Change from baseline by visit/timepoint will also be reported using the number of subjects with the reported value, mean, median, SD, minimum value, maximum value, and inner quartile percentiles. Subjects with missing data for a given visit will not contribute to the tabulations for that visit.

9.5.3 Clinical Laboratory Test Results

Laboratory test results will be listed with each out of range value classified as low (L) or high (H) according to the laboratory-supplied reference ranges or defined reference range for the study.

Results will be summarized in tabulations by treatment group and visit/timepoint using descriptive statistics where applicable for quantitative laboratory measurements.

Tables showing shift from baseline will also be presented.

The presence of antibodies, where detected, will be summarized descriptively and/or graphically presented. Further details will be provided in the SAP.

9.5.4 Physical Examination and Safety ECG Findings

All physical examination results will be listed.

Changes from Screening in PE and ECG results will be listed by subject for all subjects in the SAF. Height and weight will be summarized by summary statistics. The number of baseline abnormal findings and the percentage of subjects with abnormalities will be reported. A table will be provided, to report findings that represent changes from the baseline condition at each visit (for PE this table will be subdivided by each of the body systems).

9.5.5 Previous and Concomitant Medication

Previous and concomitant medications will be coded with the World Health Organization's Drug Dictionary (WHO-Drug). Previous medication (medication history) is defined as drugs and therapies taken before first dosing. Concomitant medication is defined as drugs and therapies used after first dosing, including those that started before dosing and continued after dosing.

All previous and concomitant medications will be listed by subject.

9.5.6 Statistical Analysis of Pharmacokinetics

Individual subject concentrations of TIMP-GLIA will be listed by subject and summarized by study phase (Part A, Part B), dose level, and scheduled sample time (nominal time) and study day.

Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, maximum and geometric mean) will be used to summarize TIMP-GLIA concentrations at each scheduled time, as well as derived pharmacokinetic parameters.

Graphics for TIMP-GLIA concentrations, including mean concentration-time profiles, individual subject concentration-time profiles (both linear and logarithmic-linear) and overlay ("spaghetti") plots of concentrations-time profiles will be produced as appropriate overall and by study phase (Part A, Part B) and dose level. Presentation taking into account dose (mg) administered may also be included, as appropriate.

9.6 Missing or Outlier Data

Missing values for safety data (except for dates) will not be imputed. Missing or partial dates will be imputed as described in the SAP.

As a general principle, no imputation of missing data will be done. Incomplete data for AEs (e.g., partial dates) and inaccurate data for laboratory parameters (e.g., values below the lower limit of quantification, LLOQ) will be considered for imputation.

TIMP-GLIA concentration values below the LLOQ will be set to zero for calculation of summary statistics. If one or more values are less than the LLOQ, the geometric mean will not be calculated. The handling of missing concentration data points, below the LLOQ data points, outlier data points, and individual outlier PK parameter values will be described in the SAP.

Further details will be provided in the SAP.

9.7 Interim Analysis

Interim data locks for data collected through the end of the investigational period (Day 60) may be performed and after each part of study so that the key data can be reviewed and reported. Datasets affected by data availability during the follow-up period will be augmented. Details will be provided in the SAP.

10 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

10.1 Procedure for Clinical Study Quality Control and Study Management

10.1.1 Data Collection/Documentation

All procedures conducted under the protocol must be documented. For screening failures, the minimum demographic data (sex, birth date, race and informed consent date), outcome of eligibility assessment (inclusion and exclusion criteria), reason for screening failure and AEs details must be document within the source.

The investigator or designee will be responsible for case report form completion and that all data and queries are accurate, complete and are verifiable with the source. The source should be appropriately maintained by the clinical unit.

Electronic case report forms (eCRFs) and any supporting documents should be available for review/retrieval by the sponsor/designee at any given time.

10.1.2 Specification of Source Documents

Source data may be paper and/or electronic and must be available at the clinical unit to document the existence of the study subjects and to substantiate protocol adherence and integrity of study data. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included within the source records:

1. Demographic data (date of birth [DD MMM YYYY], sex, race, ethnicity, height and body weight, BMI),
2. Inclusion and exclusion criteria details,
3. Participation in clinical study and signed and dated informed consent forms,
4. Visit dates,
5. Medical and medication history and physical examination details,
6. Key pharmacokinetic and safety data (including dates and times of scheduled and unscheduled procedures, events, tests),
7. AEs and concomitant medication (if applicable),
8. Results and medical interpretation of relevant examinations,
9. Laboratory printouts (if applicable),
10. Detailed record of receipt, dispensing, and final disposition of study drug, and study drug storage conditions,
11. Administration of study drug details including administration conditions,
12. Reason for premature discontinuation (if applicable),

13. Subject ID number and randomization number (if applicable),
14. A record of the pharmacokinetic sample processing and storage history, including date/time each sample is transferred to the freezer, freezer identification and the temperature log for the freezer,
15. Records of clinical study-related telephone conversations with clinical study subjects (e.g., AEs, concomitant medications, well-being), ad hoc medical consultation pertaining to study subjects.

10.1.3 Clinical Study Monitoring

The sponsor or delegated contract research organization (CRO) is responsible for monitoring the clinical study to ensure that subject's human rights, safety and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures. This includes verifying that the FDA Form 1572 and site signature log and PI's delegation of responsibility log and other regulatory documents are current, and that any protocol deviations are documented with appropriate notifications made (e.g., sponsor, IRB, regulatory authorities) in a timely manner. Monitoring will include a combination of procedural verification (e.g., study drug preparation, timing of procedures) as well as source data verification (e.g., reconciliation of source data to (e)CRFs, verification of study records for GCP compliance) as appropriate.

It is important that the investigator and other study personnel are available during the monitoring visits to support clinical study monitoring.

10.1.4 Direct Access to Source Data/Documents/Inspection of Records

The investigator must permit monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/independent ethics committee (IEC) and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents, when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access. The sponsor or designee monitor will not collect individually identifying information (e.g., name, address, social security number) on trial participants.

The auditor or inspector may ask to visit the facilities where procedures are performed, records are collected, where the study drug is stored and prepared, and any other facility used during the study. In the event of an audit, investigator agrees to allow the sponsor, representatives of the sponsor, the FDA, or other regulatory agency access to inspect relevant facilities.

If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately.

10.1.5 Data Management

Data Management will be coordinated by the designee of the sponsor and the designee's procedures and documentation policies will be followed. All study-specific processes and definitions will be documented by Data Management. Coding of medical terms and medications will be performed using MedDRA and WHO-Drug respectively.

10.1.6 Protocol Deviations

A protocol deviation is an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A significant deviation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the subject when the subject or investigator has failed to adhere to significant protocol requirements. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or when there is nonadherence to FDA or other applicable regulations and/or ICH E6(R2) guidelines.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to sponsor are defined as any unplanned incidents involving noncompliance with the final approved protocol, including but not limited to, any subject who:

- Protocol deviation 1 – Entered the study even though they did not satisfy entry criteria
- Protocol deviation 2 – Developed withdrawal criteria during the study and was not withdrawn
- Protocol deviation 3 – Received wrong treatment or incorrect dose
- Protocol deviation 4 – Received excluded concomitant treatment

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor or designee will follow-up with the investigator, as applicable, to assess the deviation and the possible impact on the safety and/or pharmacokinetic parameters of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the sponsor or designated Clinical Contact *immediately*.

The investigator will also assure that deviations meeting IRB's and applicable regulatory authorities' criteria are documented and communicated appropriately to the IRB and applicable regulatory authorities. All documentation and communications to the IRB and applicable regulatory authorities will be provided to the sponsor or designee and maintained within the trial master file.

NOTE: Other deviations outside of the categories defined above that are required to be reported to the IRB in accordance with local requirements will be reported, as applicable.

10.1.7 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB and, if applicable, to the appropriate regulatory authorities for approval before subjects can be enrolled into an amended protocol.

10.1.8 End of Trial in All Participating Countries

The end of the clinical study is defined as the last subject's last study visit (late follow-up visit).

10.2 Ethics and Protection of Subject Confidentiality

10.2.1 Institutional Review Board/Ethics Committee/Regulatory Authorities

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the investigator's brochure, the informed consent form(s) and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB/IEC. The IRB/IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB/IEC approval of the protocol, informed consent form(s) and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IRB/IEC approval prior to implementation of the changes. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible ethics committees and regulatory agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IRB/IEC of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IRB/IEC should also be provided to the sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IRB/IEC at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC within the applicable requirements.

10.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki (1996).

10.2.3 Informed Consent of Subjects

The requirements of the informed consent are described in Appendix 13.2.

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed informed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor, regulatory authorities and other applicable individuals upon request.

10.2.4 Subject Confidentiality

Individual subject medical information obtained because of this study is considered confidential.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials, sex, and date of birth (or year of birth as per local requirement) will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory authorities to review and/or to copy any medical records relevant to the study.

The sponsor will ensure that the use and disclosure of protected health information obtained during a US research study is consistent with federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act).

10.3 Insurance and Compensation for Injury

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

10.4 Publication, Disclosure, and Clinical Trial Registration Policy

10.4.1 Use of Study Information and Publication of Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the investigator's brochure and other pertinent information is confidential and remains the property

of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information only for the purpose of the study. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

10.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Cour will, at a minimum register all applicable clinical trials conducted in subjects that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation.

10.4.3 Clinical Trial Results Disclosure

Cour will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

11 INVESTIGATOR'S OBLIGATIONS

This study will be conducted according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix 13.4.

11.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate (e)CRFs and source documentation as part of the case histories. These source documents include laboratory reports and original ECGs, and electronic capture that will be used to record study data. The sponsor's representative will supply the (e)CRF.

11.2 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

11.3 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to his/her IRB/IEC as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

11.4 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome, and the sponsor and regulatory authority(ies) with any reports required.

11.5 Clinical Study Report

The ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final clinical study report which forms part of a marketing authorization application be signed by the coordinating investigator or the principal investigator(s). The coordinating investigator (representative investigator) or principle investigator will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. For multicenter studies, the coordinating investigator (representative investigator) may be selected from the participating investigators by the sponsor prior to database lock.

11.6 Records Retention

The investigator will archive all study data (e.g., subject identification code list, source data, (e)CRFs [if applicable] and investigator's file) generated by the methods described in the protocol and relevant correspondence. Data will be recorded in the subjects' medical records and/or study progress notes and source documentation.

Essential 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

The sponsor or designee will archive and retain all documents pertaining to the study (trial master file) according to local regulations.

The documents and the judgments of any committee outside the study sites (e.g., minutes and SOPs and others), if applicable, shall be retained by the sponsor or designee.

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13 APPENDICES

13.1 Liver Safety Monitoring and Assessment (Drug Induced Liver Injuiry, DILI)

Any subject enrolled in a clinical study with active drug therapy that reveals an increase of serum aminotransferases > 3 x ULN or bilirubin > 2 x ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP and TBL). Testing should be repeated within 48 to 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormalities to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**TBL**
Moderate	> 3 x ULN	or	> 2 x ULN
Severe†	> 3 x ULN	and	> 2 x ULN

† Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant). The 2 "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 x ULN ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and International Normalized Ratio (INR) > 1.5 (if INR testing is applicable/evaluated).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver test (LT) results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The investigator or designee should complete a liver abnormality case report form (LA-CRF) or collective of appropriate CRFs capturing required

information, and/or another appropriate document (e.g., liver abnormality source document(s)). Subjects with confirmed abnormal LT results should be followed up as described below.

Confirmed moderately abnormal LTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as an SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases should be recorded as "AEs" on the AE page within the source. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients, and may be associated with fluctuating aminotransferase (AT) levels. The investigator should ensure that the medical history documentation captures any illness that predates clinical study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, should be entered on the concomitant medication page within the source. Information on alcohol, other substance use and diet should be entered on the LA-CRF or collective of appropriate CRFs and/or other appropriate documents (e.g., liver abnormality page(s) from the source).
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other clinical laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or collective of appropriate CRFs and/or other appropriate documents (e.g., liver abnormality page(s) from the source).

<u>Study Subject Discontinuation</u>

In the absence of an explanation for increased LTs, such as viral hepatitis, preexisting or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Alternatively, the investigator may determine that it is in the subject's best interest to continue study enrollment to undergo planned and additional medical

supervision and testing to adequately follow up the subject's condition. Discontinuation of treatment should be considered if:

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and TBL > 2 x ULN or INR > 1.5 (if INR testing is applicable/evaluated).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring of a subject with moderate or severe hepatic laboratory tests is not possible, study drug should be discontinued.

References

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3

Guidance for Industry titled "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

13.2 Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a. that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Cour and business partners assisting Cour, its affiliates, and licensing partners; (2) regulatory agencies and other health authorities; and (3) IRBs/IECs;
    b. that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    c. that the subject's identity will remain confidential in the event that study results are published.
24. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

13.3 Windows For PK Blood Sample Collection

Nominal Time Relative to Infusion Start	Window
Predose (0 hour)	Within 15 minutes prior to dose start
Post dose Part A ≤ 35 minutes	± 1 minute
1 hour	± 3 minutes
2 hours	± 6 minutes
Post Dose Part B – end of infusion	± 6 minutes
4 hours	± 12 minutes
6 hours	± 18 minutes
8 hours	± 24 minutes
10 hours	± 30 minutes
12 hours	± 36 minutes
14 hours	± 42 minutes
24 hours	± 72 minutes
36 hours	± 108 minutes
48 hours	± 144 minutes
≥ 144 hours	± 24 hours

Blood samples for PK should be collected as soon as possible to the scheduled time relative to **infusion start time**. In the event of an interference, PK collections within the windows above will not be considered protocol deviations.

Reasons that a collection fell out of the windows above must be identified in the source documentation.

Actual time elapsed from dose start will be used for PK calculations.

Nominal times in bold, black font apply to the study. Nominal times in gray font are not scheduled for this study and are only shown to provide context.

13.4 Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities by signing a "Statement of Investigator" Form FDA1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study-specific screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including (e)CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

13.5 Amendment 1: Summary of Changes To Protocol Version 1.0

The final protocol TGLIA-5.001 version 1.0 dated 18 Jul 2017 has been revised to version 2.0 dated 28 Aug 2017 to include substantantial and nonsubstantial (administrative) changes as detailed in the table below.

SUBSTANTIAL CHANGES

Description of Change	**Affected Section(s) in Amended Protocol Version 2.0**
Design – Enrollment for Dose Escalation Cohorts Accelerated titration design for the first 2 dose levels of Part A was changed from 1+1 to 2+2. Cohorts of 2 subjects will be enrolled at dose level 1 and dose level 2. If dose-limiting toxicity (DLT) occurs in 1 of the subjects, the Safety Committee may expand enrollment at the same dose level by 2 subjects.	Synopsis, Study Design, Dose Escalation Part A Synopsis, Safety Committee Synopsis, Selection of Study Population Figure 1. Schematic of Planned Dosing Section 2.1 Overview of Study Design Section 2.3 Rationale for the Trial Design Section 4.0 Study Population Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Design – Cohort Expansion Beyond the 2+2 and 3+3 cohort expansions in the event of a DLT, a provision was added to allow the Safety Committee to expand a dose cohort up to a total of 12 subjects to better define the relationship between dose and emerging safety signals.	Synopsis, Study Design, Dose Escalation Part A Synopsis, Study Design, Part B Synopsis, Safety Committee Section 2.1 Overview of Study Design, Dose Escalation Part A Section 2.1 Overview of Study Design, Part B Section 7.2 Safety Committee Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Description of maximum tolerable dose (MTD) Was: If no more than 1 subject experiences a DLT in each of the planned dose cohorts, the highest tested dose will be the MTD. In the context of the cohort expansions, the description has been revised such that the highest dose level that did not cause unacceptable side effects will be considered the MTD.	Section 7.3.3 Dose Escalation – Dosing Subjects At the Next Dose Level
Planned Number of Subjects Because each of the first 2 dose levels will enroll at least 2 subjects, the planned enrollment for Part A increased from 17 to 19 subjects and the overall planned enrollment for the study increased from 20 to 22 subjects.	Synopsis, Study Design, Part A Synopsis, Selection of Study Population Section 2.1 Overview of Study Design, Part A Section 4.0 Study Population
Design – Staggering of Individual Subject Dosing, Part A	Synopsis, Study Design, Part A Section 1.5 Benefit-Risk Assessment (solid bullet

Description of Change	Affected Section(s) in Amended Protocol Version 2.0
The time between dosing successive subjects was increased from 24 hours to 168 hours (7 days).	items 8 and 9) Section 2.1 Overview of Study Design, Part A Section 2.3 Rationale for the Trial Design Section 6.3 Method of Assigning Subjects to Treatment Groups Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Design – Staggering of Individual Subject Dosing, Part B The time between dosing successive subjects was increased from 24 hours to 168 hours (7 days) after the second dose. The staggering interval will be applied between all subjects enrolled in Part B. Subjects in Part B may not be dosed on the same day.	Synopsis, Study Design, Part B Section 2.1 Overview of Study Design, Part B Section 2.3 Rationale for the Trial Design Section 6.3 Method of Assigning Subjects to Treatment Groups Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Design –Dose Escalation Interval The dose escalation interval was increased from 48 hours to 168 hours (7 days). Therefore, the last subject enrolled in a dose cohort will be observed and data collected for at least 168 hours (7 days) before the Safety Committee will consider the progression or termination of dosing.	Synopsis, Study Design, Dose Escalation Part A Section 1.5 Benefit-Risk Assessment (solid bullet items 10 and 11) Section 2.1 Overview of Study Design, Dose Escalation Part A Section 2.3 Rationale for the Trial Design Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort) Section 7.3.3 Dose Escalation – Dosing Subjects At the Next Dose Level
Design- Progression from Part A to Part B The minimum available safety data from the last cohort in Part A increased from 48 hours to 168 hours (7 days) for evaluation by the Safety Committee.	Synopsis, Study Design, Dose Escalation Part A Section 2.1 Overview of Study Design, Dose Escalation Part A
Safety Committee To ensure independence of the Safety Committee, the Cour medical monitor will not be a member. The sponsor medical monitor will be available by telephone to answer data questions that arise but otherwise will not be present for the Safety Committee meeting and decision-making process.	Synopsis, Safety Committee Section 7.2 Safety Committee
Dose Stopping Rules An additional dose stopping rule was added. Dosing of additional subjects in a cohort will also be stopped upon the occurrence of 2 or more of the same CTCAE Grade 3 toxicity (among total subjects dosed) or the first occurrence of a CTCAE Grade 4 or Grade 5	Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)

Description of Change	Affected Section(s) in Amended Protocol Version 2.0
toxicity, irrespective of relationship to study drug. At such time the toxicity will be investigated by the Safety Committee to determine whether the study can resume or if the Study Stopping Criteria were met.	
Visits In Part A, the Day 14 (+/- 2 days) visit was changed from a telephone contact visit to an outpatient visit so that safety tests and assessments could be performed. Another outpatient visit at Day 60 (+/-3 days) was added. Telephone contact visits (regarding the subject's diet, well-being, occurrence of adverse events, and concomitant medication use) by a health care practitioner were added at Day 90, Day 120 and Day 180 (all +/- 3 days). In Part B an outpatient visit at Day 60 (+/-3 days) was added so that safety tests and assessments could be performed. Telephone contact visits (regarding the subject's diet, well-being, occurrence of adverse events, and concomitant medication use) by a healthcare practitioner were added at Day 90, Day 120 and Day 180 (all +/- 3 days).	Synopsis, Exploratory Objective Synopsis, Duration of Study Period Table 1. Schedule of Procedures Part A Table 2. Schedule of Procedures Part B Section 2.1 Overview of Study Design, Duration of Study Section 2.3 Rationale for the Trial Design Section 3.1.3 Exploratory Objective
Tests Sampling for an additional test, C1q binding for immune complex detection, was added at: predose Day 1 (for Parts A and B), predose Day 8 (for Part B), Day 14 +/-1 day (Parts A and B), Day 30 +/- 2 days (for Part A) or Day 38 +/- 2 days (for Part B) and Day 60 +/- 3 days (Parts A and B).	Synopsis, Endpoints, Safety and Tolerability Table 1. Schedule of Procedures Part A Table 2. Schedule of Procedures Part B Section 3.2. Endpoints Section 8.5.6.4 Immunogenicity (Anti-Gliadin Antibodies) and Immune Complex Formation
Tests Sampling timepoints for anti-drug antibody testing (as deaminated gliadin peptide [DGP]-specific antibody IgG) were added at: Day 14 +/-1 day (Parts A and B) and Day 60 +/- 3 days (Parts A and B).	Table 1. Schedule of Procedures Part A Table 2. Schedule of Procedures Part B
Tests Sampling timepoints for cytokine testing were added at: 24 hours post dose (i.e., Day 2) (Parts A and B) and 24 hours post dose (i.e., Day 8) (Part B).	Synopsis, Endpoints, Safety and Tolerability Table 1. Schedule of Procedures Part A Table 2. Schedule of Procedures Part B Table 9. Clinical Laboratory Tests (footnote b) Section 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction - Cytokines

Description of Change	Affected Section(s) in Amended Protocol Version 2.0
Tests – Prioritization for Dose Escalation Decision Cytokine results will be evaluated for dose escalation decision. The planned cytokine tests were reviewed and those needed for dose escalation decision were identified (i.e., TNF-α, IFN-γ, IL-2, IL-8, IL-10). The analyses for the other cytokines can be performed at the end of the study.	Synopsis, Study Design, Part A Synopsis, Safety Committee Synopsis, Endpoints, Safety and Tolerability Section 1.5 Benefit-Risk Assessment (solid bullet item 10) Section 2.1 Overview of Study Design, Part A Section 2.3 Rationale for the Trial Design Section 3.2. Endpoints Section 7.2 Safety Committee Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort) Section 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction - Cytokines
Approximate Total Amount of Blood for Scheduled Tests The approximate total amounts of blood drawn for scheduled tests were revised to take into account the additional visits and blood draws and also the volumes needed with prioritized multiplex assay of analytes for dose escalation decision vs. samples that could be batch tested at the end of the study. The net changes in approximate total volume were an increase in Part A from 301 mL to 320 mL and decrease in Part B from 463 to 445 mL.	Section 8.8 Total Amount of Blood

NONSUBSTANTIAL (ADMINISTRATIVE) CHANGES

Description of Change	Affected Section(s) in Amended Protocol Version 2.0
Study Stopping Rules The word “Study” was added to “Study Stopping Rules” in the section heading and cross references to ensure distinction in purpose from dose stopping conditions. The study will be terminated if the Safety Committtee determines that the Study Stopping Rules have been met.	Synopsis, Study Design, Dose Escalation Part A Synopsis, Study Stopping Rules Synopsis, Safety Committee Section 1.5 Benefit-Risk Assessment (solid bullet item 9) Section 2.1 Overview of Study Design, Dose Escalation Part A Section 2.3 Rationale for the Trial Design Section 5.2 Discontinuation of the Study Section 7.2 Safety Committee Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort) Section 7.3.3 Dose Escalation – Dosing Subjects At

Description of Change	Affected Section(s) in Amended Protocol Version 2.0
	the Next Dose Level Section 7.3.6 Study Stopping Rules
Correction of Cytokine Test Names IFN-δ (IFN-delta) was corrected to IFN-γ (IFN-gamma). Because IFN-γ is a cytokine test specified for safety monitoring it was important to correct this typographical error to ensure the correct test would be performed. Fractaline was corrected to fractalkine. Because fractalkine is a cytokine test specified for safety monitoring it was important to correct this typographical error to ensure the correct test would be performed.	Synopsis, Endpoints, Safety and Tolerability Section 3.2 Endpoints Table 9 Clinical Laboratory Tests Section 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction - Cytokines
Clarification of Anti-Gliadin-Antibody (Anti-Drug Antibody) Test Clarification that deamidated gliadin peptide (DGP)-specific IgG antibody will be the anti-drug antibody test for TIMP-GLIA was added. The abbreviation AGA for "anti-gliadin antibody" test was deleted where it was listed separately from the deamidated gliadin peptide (DGP) test.	Synopsis, Endpoints, Safety and Tolerability Table 1. Schedule of Procedures Part A Table 2. Schedule of Procedures Part B Section 3.2 Endpoints Section 8.3 Diet History Table 9 Clinical Laboratory Tests Section 8.5.6.4 Immunogenicity (Anti-Gliadin Antibodies) and Immune Complex Formation
Clarification of Endpoint Categories for Consistency with Synopsis For consistency with the Synopsis and to avoid mischaracterization of the revisions implemented in Section 3.2 Endpoints via Amendment 1: Subsection 3.2.1 "Primary Endpoint" was renamed "Safety and Tolerability Endpoints" Subsection 3.2.2 "Secondary Endpoints" was renamed "Pharmacokinetic Endpoints" Subsection 3.2.3 "Exploratory Endpoints" was omitted because anti-gliadin antibody to TIMP-GLIA (i.e. anti-drug antibody) is included within "Safety and Tolerability Endpoints".	Section 3.2 Endpoints

13.6 Amendment 2: Summary of Changes To Protocol Version 2.0

The final protocol TGLIA-5.001 version 2.0 dated 28 Aug 2017 incorporating Amendment 1 has been revised to version 3.0 dated 30 Aug 2017 to include substantantial and nonsubstantial (administrative) changes as detailed in the table below.

SUBSTANTIAL CHANGES

Description of Change	**Affected Section(s) in Amended Protocol Version 3.0**
Laboratory Assessments Urine protein-to-creatinine ratio (UPCR) [using spot urine samples] was added to routine urine testing to enhance monitoring of kidney function.	Table 9 Clinical Laboratory Tests List of Abbreviations and Definition of Key Terms Table 1 Schedule of Procedures Part A (and footnotes) Table 2 Schedule of Procedures Part B (and footnotes)
Laboratory Assessments A 24-hour urine collection may be ordered at the investigator's discretion to follow up an abnormal UPCR indicating protein in the urine.	Section 8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety
Laboratory Assessments/Screening A clarification was added that women with postmenopausal status confirmed by screening follicle stimulating hormone (FSH) test result need not undergo subsequent urine pregnancy testing.	Synopsis Exclusion Criterion #16 Table 1 Schedule of Procedures Part A (and footnotes) Table 2 Schedule of Procedures Part B (and footnotes) Section 4.2 Exclusion Criteria, Criterion #16 Section 8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety
Laboratory Assessments To enhance evaluation of the immune response to TIMP-GLIA, measurement of IL-1β, IL-4, IL-5, and IL-13 are added to the cytokine panel. These results are not required for dose escalation decision but may be analyzed and reported at the end of each dose cohort if they are included in the multiplex assay with TNF-α, IFN-γ, IL-2, IL-8, and IL-10.	Synopsis, Endpoints, Safety and Tolerability List of Abbreviations and Definition of Key Terms Section 3.2.1 Safety and Tolerability Endpoints Table 9 Clinical Laboratory Tests Section 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction - Cytokines
Eligibility The upper limit for body mass index (BMI) was increased from 30 kg/m^2 to 32 kg/m^2	Synopsis Inclusion Criterion #4 Section 4.1 Inclusion Criteria, Criterion #4
Eligibility The time restriction for high dose inhaled corticosteroids [>960 µg/day of beclomethasone dipropionate or equivalent] "within 30 days of Day 1" was added.	Synopsis Exclusion Criterion #6c Section 4.2 Exclusion Criteria, Criterion #6c

Description of Change	Affected Section(s) in Amended Protocol Version 3.0
Final visit safety assessments Whenever possible, all subjects who withdraw from the study prematurely are to undergo all final visit safety assessments. For clarity these assessments were specified to include those listed in the *Schedules of Procedures* for Study Day 14 of Part A or Part B, as applicable.	Table 1 Schedule of Procedures Part A (and footnotes) Table 2 Schedule of Procedures Part B (and footnotes)

NONSUBSTANTIAL (ADMINISTRATIVE) CHANGES

Description of Change	Affected Section(s) in Amended Protocol Version 3.0
Dosing Procedure Clarification that subjects should remain supine during dosing was added.	Table 1 Schedule of Procedures Part A footnote Table 2 Schedule of Procedures Part B footnote Section 7.1 Dose and Regimen
Correction in Table 9 Clinical Laboratory Tests Hepatitis B core antibodies (Anti HBc) listed under "Hepatitis & HIV Serology" was deleted. It is not a required test for this study.	Table 9 Clinical Laboratory Tests
Clarification in Table 9 Clinical Laboratory Tests The subheading to distinguish coagulation tests for follow-up of potential anaphylaxis/anaphylactoid reaction was updated to "Predose &" PRN only (a).	Table 9 Clinical Laboratory Tests
The statement was updated to specify that "applicable" clinical trials will be registered in accordance with applicable law, regulation, and guidance.	Section 10.4.2 Clinical Trial Registration
Misspelling of health care "practioner" was corrected to "practitioner"	Table 1 Schedule of Procedures Part A footnote Table 2 Schedule of Procedures Part B footnote
Exploratory Objective CCI [redacted]	Synopsis Exploratory Objective Section 3.1.3 Exploratory Objective

13.7 Amendment 3: Summary of Changes To Protocol Version 3.0

The final protocol TGLIA-5.001 version 3.0 dated 30 Aug 2017 incorporating Amendment 2 has been revised to version 4.0 dated 16 Oct 2017 to include substantantial and nonsubstantial (administrative) changes as detailed in the table below.

SUBSTANTIAL CHANGES

Description of Change	**Affected Section(s) in Amended Protocol Version 4.0**
A minimum body weight of 33 kg was added to the requirement of BMI of >16 kg/m^2. The maximum BMI of 32 kg/m^2 was replaced with a maximum body weight of 129 kg. The requirement that subjects who are underweight or overweight or obese must be otherwise healthy in the opinion of the investigator remains unchanged. This adjustment prevents unnecessary exclusion of otherwise healthy patients of smaller or larger stature in the celiac disease community. In addition, the minimum and maximum weights provide consistency with the pharmacy manual dose calculations for subjects whose stature may be at the extremes.	Synopsis Inclusion Criterion #4 Section 4.1 Inclusion Criterion #4
The duration of no known gluten exposure was reduced from "approximately 2 months prior to enrollment" to "at least 10 days prior to the Screening Visit." The antigen-specific IgG response to gluten would generally peak at ~2 weeks and would last for ~4-5weeks. Therefore, a bonafide immune response to the gluten intake would be identified by the screening celiac serology testing. In addition, a predose DGP-specific IgG will be recorded to capture the change from the screening value and to set the predose baseline.	Synopsis Inclusion Criterion #5c Section 4.1 Inclusion Criterion #5c Section 8.3 Diet History
The criterion was revised such that either a weak positive or negative celiac serology value is acceptable (either tTG-specific IgA or, for IgA-deficient subjects, DGP-specific IgG). The study does not include a gluten challenge that would necessitate an optimization of the pre-challenge conditions. Relaxing the criterion is not expected to alter safety or tolerability and should facilitate recruitment.	Synopsis Inclusion Criterion #5d Section 4.1 Inclusion Criterion #5d
Consumption of alcohol will be prohibited from 24 hours prior to clinic admission (when testing for presence of alcohol will be performed) until discharge from the clinic. Updates were made to ensure that exclusion criterion 13 is consistent with the body of	Synopsis Exclusion Criterion #13 Section 4.2 Exclusion Criterion #13 Section 7.6.2 Dietary and Fluid Restricions

Description of Change	Affected Section(s) in Amended Protocol Version 4.0
the protocol pertaining to dietary and fluid restrictions.	
A 28-day exclusion for an inactive vaccine was added consistent with the exclusion for a live vaccine. This was for simplicity and consistency in approach since both an inactive and live vaccine contain viral particles as opposed to the subunit vaccine which contains viral protein.	Synopsis Exclusion Criterion #21 Section 4.2 Exclusion Criterion #21

NONSUBSTANTIAL (ADMINISTRATIVE) CHANGES

Description of Change	Affected Section(s) in Amended Protocol Version 4.0
The name of the Clinical Research Contact, Trial Manager and the name and role of the *Recruitment and* Enrollment Coordinator were updated to reflect current assignments by the study CRO.	Title page
The reference to ICH E6 was updated from "R1" to "R2" for consistency with Sections 10.1.6 and 11.2.	Title page
The planned study duration was increased from 1Q to 3Q 2018 to reflect the increased duration between dosing subjects and follow up visits.	Protocol Synopsis, Study Duration
A typographical error regarding duration of study for an individual subject in Part B was corrected from "up to 99 days" to "up to 91 days" reflecting the maximum 28-day screening period and 60 (+3 days)-day investigational period.	Protocol Synopsis, Study Design, Duration of Study Period Section 2.1 Overview of Study Design, Duration of Study
The typographical error of 0.25 mg/kg was corrected to 0.1 mg/kg in the figure legend.	Figure 1 Schematic of Planned Dosing, Part A and Part B
Format change to header rows of the respective *Schedules of Procedures* for Parts A and B such that "Investigational Period" continues through the Day 60 visit, consistent with its definition as per the Definition of Key Terms.	Table 1 Schedule of Procedures Part A Table 2 Schedule of Procedures Part B
Residual references to the enrollment of 1 subject in the accelerated titration portion of Part A were changed to 2 subjects. Residual descriptions of a 1+1 accelerated titration were updated to 2 + 2 as per Amendment 1.	Section 2.5.3 TIMP-GLIA Maximum Recommended Starting Dose Table 7 Planned Dose Levels and Rationale Section 4.0 Study Population Section 7.2 Safety Committee Section 7.3.4 Dose Reduction
"Prior to study initiation" was removed. Drug will be supplied on demand by Cour or its designee prior to subject dosing.	Section 6.2.3 Inventory and Accountability

Description of Change	**Affected Section(s) in Amended Protocol Version 4.0**
A clarification was added that the sponsor's designee will "confirm" (rather than assign) the 9-digit unique subject ID number when a site has requested enrollment of an eligible subject. The site will follow the subject ID numbering convention described in this section of the protocol.	Section 6.3 Method of Assigning Subjects to Treatment Groups
A cross reference to Section 8.6.1 which contains a description for when an abnormal laboratory value constitutes an AE, was added for clarification.	Section 8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety
Urine testing for drugs of abuse and alcohol was separated using a bullet for clarification.	Section 8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety
Addition to Table 9 Clinical Laboratory Tests C1q binding was listed under "Additional Tests" for consistency with the *Schedules of Procedures* for Parts A and B and with Section 8.5.6.4.	Table 9 Clinical Laboratory Tests
A statement was added that a presentation of data by dose (mg) administered may be added, if appropriate.	Section 9.5 Safety Analysis Section 9.5.6 Statistical Analysis of Pharmacokinetics

13.8 Amendment 4: Summary of Changes To Protocol Version 4.0

The final protocol TGLIA-5.001 version 4.0 dated 16 Oct 2017 incorporating Amendment 3 has been revised to version 5.0 dated 1 Dec 2017 to include substantantial and nonsubstantial (administrative) changes as detailed in the table below.

NOTE: Amendment 4 was not reviewed by any IRB/IEC and was not implemented at any clinical sites.

SUBSTANTIAL CHANGES

Description of Change	**Affected Section(s) in Amended Protocol Version 5.0**
Healthy subjects were included as a population in which the primary and secondary study objectives are being explored.	Synopsis, Primary Objective and Secondary Objectives Section 3.1.1 Primary Objective Section 3.1.2 Secondary Objectives
The text of the study design description was revised to specify inclusion of healthy subjects to the study. It was also specified that cohorts from each population will proceed through the study at their own rate, contingent upon enrollment rate and safety reviews by the Safety Committee. Cross references to the schematics of planned dosing of healthy subjects were added. Enrollment of 19 healthy subjects in Part A and of 3 subjects in Part B was specified. Possibilities for healthy subject cohort expansion in the event of DLT or to better investigate the relationship between dose and emerging safety signals (in the same manner as for CD cohorts) were described.	Synopsis, Study Design Section 2.1 Overview of Study Design, Part A and Part B
The procedure for staggering individual healthy subject doses by a minimum 48-hour wait period was described.	Synopsis, Study Design Section 2.1 Overview of Study Design, Part A and Part B Section 1.5 Benefit-Risk Assessment Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Clarification was added that decisions regarding progression or termination of dosing will be made separately for each population (CD or healthy subjects) based upon the respective safety data.	Synopsis, Study Design Section 2.1 Overview of Study Design, Part A Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Clarification that the up to 91-day duration of study in Parts A and B pertains to the *investigational period* was added for CD subjects. Total duration of the study investigational period for	Synopsis, Duration of Study Period Section 2.1 Overview of Study Design, Duration of Study Period

Description of Change	Affected Section(s) in Amended Protocol Version 5.0
Parts A and B for healthy subjects was added.	
The rationale for adding healthy subject cohorts was added. The rationale for including CD subjects with respect to presence of gliadin-specific T-cells was refined.	Section 2.4 Rationale for the Subject Population
Enrollment of 22 male and female healthy subjects across the clinical sites was added. Clarification that healthy subjects who withdrew from study prior to dosing was added. Redundant text was deleted.	Synopsis, Selection of Study Population Section 4.0 Study Population
"CD" was added to each criterion in the existing lists of inclusion and exclusion criteria to distinguish them from the newly added eligibility criteria for healthy volunteers.	Synopsis, Eligibility Criteria, Inclusion Criteria, CD Subjects and Exclusion Criteria, CD Subjects Section 4.1.1 Inclusion Criteria for Subjects With CD Section 4.2.1 Exclusion Criteria for Subjects With CD
Splenectomy was added to CD subject exclusion criterion #3	Synopsis, Eligibility Criteria, Exclusion Criteria, CD Subjects Section 4.2.1 Exclusion Criteria for Subjects With CD
Separate lists of inclusion and exclusion criteria for healthy subjects was added. These were the same as the eligibility criteria specified for CD subjects with the exception of celiac disease-related requirements.	Synopsis Eligibility Criteria, Inclusion Criteria, Healthy Subjects and Exclusion Criteria, Healthy Subjects Section 4.1.2 Inclusion Criteria for Healthy Subjects Section 4.2.2 Exclusion Criteria for Healthy Subjects
The approximate volume of blood to be collected for scheduled testing from screening until the last in-clinic procedure was presented for each population in context of the study duration. The estimated blood draw volumes were slightly adjusted to 300 mL (formerly ~320 mL) for CD subjects in part A and ~500 mL (formerly ~ 445 mL) CD subjects in part B. Because screening celiac serology and HLA typing is not needed, the volume is approximately 11 mL less for healthy subjects in either part of the study.	Section 8.8 Total Amount of Blood
A general statement was added at the beginning of the section that TLFs and methods will be performed for each study population.	Section 9.0 Statistical Methods
The word "patient" was substituted with "subject" to make the section more inclusive to both populations in the study.	Section 9.4 Subject Disposition
Text describing the potential interim analyses was	Section 9.7 Interim Analysis

Description of Change	Affected Section(s) in Amended Protocol Version 5.0
added (with details to be provided in the SAP).	

NONSUBSTANTIAL (ADMINISTRATIVE) CHANGES

Description of Change	Affected Section(s) in Amended Protocol Version 5.0
"and Healthy Subjects" was added to the protocol title.	Title page, protocol approval page, investigator agreement page, and synopsis
The telephone number for the Clinical Research Contact, Trial Manager was revised.	Title page
A facsimile ("fax") number was added for SAE reporting.	Title page Section 8.6.6 Collection & Reporting of SAEs
Clarification was added throughout the protocol as needed to specify which study procedures refer to both/each population(s) (CD and healthy) or which study procedures are specifically designated for subjects with CD or healthy subjects.	Throughout, including but not limited to: Synopsis, Study Design Section 2.1 Overview of Study Design, Part A and Part B Section 1.5 Benefit-Risk Assessment Section 2.2 Rationale for Tria Section 2.3 Rationale for Trial Design
Cross references to the *Schedules of Procedures*, Part A or Part B and to the schematics of planned dose cohorts were updated to include references to both the CD-specific and healthy subject-specific versions.	Throughout the document.
Clarification was added that clinic residency and visit requirements pertained to healthy subjects as specified in the corresponding *Schedules of Procedures*.	Synopsis, Clinic Residency and Visits Section 2.1 Overview of Study Design, Clinic Residency and Visits 7.6.1 Clinic Residency and Clinic Visits
Clarification was added where risks or lack thereof pertained to both healthy and CD subjects. A cross reference to the *Schedules of Procedures* for healthy subjects was added with that for the CD subjects. Additional details were provided regarding the in-vitro data relevant to the conclusion that TIMP-GLIA did not exhibit mitogenicity in PBMCs from healthy and CD donors. Rationale for the expected low risk of immune response to the gliadin in TIMP-GLIA and non-acute immune complex formation by healthy subjects was added.	Section 1.5 Benefit-Risk Assessment

Description of Change	Affected Section(s) in Amended Protocol Version 5.0
Clarification was added that the Safety Committee will monitor emerging safety data from healthy subjects and that the decision-making process pertains to both healthy volunteer and CD cohorts.	Synopsis, Safety Committee Section 7.2 Safety Committee
Clarification was added that procedures and assessments pertaining to cohort expansion or dose stopping refer to both CD and healthy subjects in Part A and Part B. Cross references to the schematics for planned dosing for healthy subjects was added.	Section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
Clarification was added that the criteria for identifying maximum tolerable dose (MTD) applies to both CD and healthy subjects.	Section 7.3.3 Dose Escalation – Dosing Subjects and the Next Dose Level
Clarification was added that Safety Committee may recommend dosing a CD or healthy cohort at a dose level that is lower than planned.	Section 7.3.4 Dose Reduction
Clarification was added that NCI CTCAE Version 4.0 (Published May 28, 2009 [v4.03: June 14, 2010]) or most current version would be used for AE grading.	Synopsis, Study Design Section 2.1 Overview of Study Design Section 8.6.3 AE Severity Assessment
Cross reference to Edition 1 of the Investigator's Brochure was expanded to include "subsequent editions as they become available."	1.3 Nonclinical Studies
The potential, in general, for reporting other cytokines (not otherwise specified) that might be included in the multiplex assay was acknowledged.	Synopsis, Endpoints, Safety and Tolerability Section 8.5.6.5 Cytokines and Laboratory Tests to Follow up Suspected Anaphylaxis/Anaphylactoid Reaction
The title of the schematic of planned dosing for celiac disease cohorts was updated to include population. A new schematic was added for healthy subject cohorts. Cross references to these 2 figures were updated.	Figure 1 Schematic of Planned Dosing in Subjects With Celiac Disease, Part A and Part B. Figure 2 Schematic of Planned Dosing in Healthy Subjects, Part A and Part B.
The titles of the *Schedules of Procedures* for celiac disease subjects, Parts A and B were updated to specify population. A clarification was added to the last item in the table legend that subjects who discontinues prematurely during the investigational period (not the follow up period) is to undergo final visit procedures. A new set of *Schedules of Procedures* was added for healthy subjects in Part A and Part B.	Table 1 Schedule of Procedures For Subjects With Celiac Disease, Part A/Part B Table 2 Schedule of Procedures For Healthy Subjects, Part A/B

Description of Change	Affected Section(s) in Amended Protocol Version 5.0
Clarification was added that the accelerated titration design would allow the study to proceed more quickly. Redundant text describing the Safety Committee review of safety data in the context of DLT and study stopping rules was deleted. Clarification was added that Day 60 is part of the investigational period applicable to both populations, whereas the long-term follow-up by telephone out to Day 180 pertains to CD subjects.	Section 2.3 Rationale for the Trial Design
Clarification was added that subjects who discontinue participation during the investigational period are to be contacted by telephone at least twice over 2 weeks. Similar due diligence is to be applied to follow up missed telephone follow up calls.	Section 5.1.1 Handling of Withdrawals
Clarification was added that standardized meals will be served to healthy subjects and gluten-free meals will be served to CD subjects while they are resident in the clinic.	Section 7.6.2 Dietary and Fluid Restrictions
Clarification was added that subjects will be distinguished within the data as healthy or CD.	Section 8.1 Demographics and Baseline Characteristics
Clarification was added that dietary history will be taken only for subjects with celiac disease.	8.3 Diet History (Subjects With Celiac Disease)
Clarification was added that if a subject discloses participation in another interventional trial during his/her participation in TGLIA-5.001, the investigational product should be recorded as a concomitant medication. Prohibition of concomitant medication was specified for healthy subjects, exception for contraceptives and stable hormone replacement therapy.	8.4 Concomitant Medications
Because CD-related testing is not applicable to healthy subjects, a more inclusive/descriptive subheading within the Table of Laboratory Tests was added, “Anti-Drug and CD-Related Serology”	Table 11 Clinical Laboratory Tests

13.9 Amendment 5: Summary of Changes To Protocol Version 6.0

The final protocol TGLIA-5.001 version 5.0 dated 1 Dec 2017 incorporating Amendment 4 has been revised to version 6.0 dated 9 Feb 2018 to include substantantial and nonsubstantial (administrative) changes as detailed in the table below.

SUBSTANTIAL CHANGES

Description of Change	**Affected Section(s) in Amended Protocol Version 6.0**
The healthy subject arm that was intended to run in parallel with the celiac disease subject arm (added via Amendment 4) has been removed. The dosing schematic, schedules of procedures, number of subjects, duration of study for healthy subjects, and text pertaining to the eligibility, objectives, and study procedures involving healthy subjects have been deleted. Minor editorial adjustments were made where necessary to accommodate the removal of the references to healthy subjects and the procedures involving healthy subjects. Also deleted for readability are references to celiac disease subjects or "CD" subjects in the context of distinguishing them from healthy subjects. Tables were renumbered owing to the removal of the healthy subject schedules of procedures Tables 3 and 4.	Throughout document, including Synopsis, Figure 2 Schematic of Planned Dosing in Healthy Subjects, Part A and Part B (deleted), Table 3 Schedule of Procedures for Healthy Subjects, Part A (deleted), Table 4 Schedule of Procedures for Healthy Subjects, Part B (deleted), Protocol sections 1.5 Benefit-Risk Assessment, 2.0 Study Design and Rationale, 3.1.1 Primary Objective, 3.1.2 Secondary Objectives, 4.0 Study Population, 6.3 Method of Assigning Subjects to Treatment Groups, 7.0 Treatment Administration, 7.6.1 Clinic Residency and Clinic Visits, 7.6.2 Dietary and Fluid Restrictions, 8.1 Demographics, 8.4 Concomitant Medications, Table 9 footnote (c), 8.8 Total Amount of Blood, 9.0 Statistical Methods.
Suspected drug-induced liver injury at least possibly related to TIMP-GLIA was added to the dose-limiting toxicity (DLT) definition. This brought forward the DILI monitoring and reporting requirments already present in Appendix 13.1 Liver Safety Monitoring and Assessment (Drug Induced Liver Injury, DILI).	Synopsis, Dose Limiting Toxicity Definition Protocol section 7.3.5 Dose Limiting Toxicity Definition
The maximum age for study eligibility was increased from 65 to 75 years.	Synopsis Selection of Study Population and Inclusion Criterion # 3 Protocol section 4.0 Study Population and Inclusion Criterion #3.
Positive HLA DQ2.5 or HLA DQ8.1 was removed as an eligibility requirement. Instead this testing will be performed for enrolled subject for information only.	Synopsis, Inclusion criterion #5b Table 1 Schedule of Procedures, Part A and Table 2 Schedule of Procedures, Part B Protocol section 4.0 Study Population, Inclusion Criterion #5b
For clarification the phrase "and for 30 days after	Synopsis, Inclusion Criterion #6

Description of Change	Affected Section(s) in Amended Protocol Version 6.0
receiving study drug" was removed from inclusion criterion #6 pertaining to practice of contraception. The criterion correctly specifies that medically approved contraception should be used throughout the study, and this phrase is unnecessary and inconsistent with the study duration. The investigational period of the study extends to Day 60 and the follow-up period to Day 180.	Protocol section 4.0 Study Population, Inclusion Criterion #6
The time that celiac symptomology will be exclusionary was reduced from within 8 weeks to within 10 days of screening. This is for consistency with the timing of no known gluten exposure in inclusion criterion #5.	Synopsis, Exclusion Criterion #2 Protocol section 4.0 Study Population, Exclusion Criterion #2
The number of days for which changes to prescription or nonprescription medication is exclusionary was reduced from 60 days to 30 days prior to Day 1.	Synopsis, Exclusion Criterion #4 Protocol section 4.0 Study Population, Exclusion Criterion #4
For clarification of exclusion criterion #6b, the descriptor "immunomodulatory" was deleted from "immunomodulatory or immune suppressing medical treatment (e.g., azathioprine, methotrexate)." In addition, the relative milestone for which this medication is exclusionary was changed from the Screening Visit to Day 1 for consistency with other medication-related criteria. For clarification of exclusion criterion #6c, the phrase "or on alternative days" with respect to prednisone regimen was removed. For consistency with the exclusionary period of other immune suppressing treatment, the time for which >20 mg daily prednisone is exclusionary was reduced from 6 months to 2 months prior to Day 1.	Synopsis, Exclusion Criterion #6b and #6c Protocol section 4.0 Study Population, Exclusion Criterion #6b and #6c
For clarification the description of exclusionary hypersensitivity was changed to "severe hypersensitivity or allergic reaction…", with individual symptoms of hypersensitivity that might or might not be severe, deleted from the criterion.	Synopsis, Exclusion Criterion #7 Protocol section 4.0 Study Population, Exclusion Criterion #7
The number of days for which acute illness is exclusionary was reduced from 28 days to 14 days, which allows reasonable time for recovery.	Synopsis, Exclusion Criterion #9 Protocol section 4.0 Study Population, Exclusion Criterion #9
Additional blood collections for anti-drug antibody IgG (as DGP-IgG) and immune complex detection by C1q binding were added: In Part A on Day 3/48	Table 1 Schedule of Procedures, Part A and Table 2 Schedule of Procedures, Part B

Description of Change	Affected Section(s) in Amended Protocol Version 6.0
hours and Day 7/144 hours post dose; In Part B on Day 3 and Day 10/48 hours and Day 7/144 hours post dose. In Part B a Day 14 collection is already scheduled so a clarification was added that it should correspond to 144 hour post (second) dose. This will provide values for gliadin antigen level (TIMP-GLIA PK), anti-drug antibody, and C1q binding at the common timepoints of predose, 48 hours, and 144 hours after each dose.	
Peripheral blood mononuclear cells will be collected at the same timepoints, i.e., predose and post dose upon appearance of symptoms of anaphylaxis/anaphylactoid reaction/cytokine release syndrome or IRR. However, the PBMCs will be used for either the ELISpot (for number of IFN-gamma and IL-10-producing T-cells) OR assay for T-cell proliferation in response to ex vivo gliadin stimulation as most appropriate and informative. If sufficient cells remain, the alternative test may be performed. This will halve the blood volume to be collected.	Protocol section 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction, Whole Blood for PBMC Isolation
New data obtained from a non-GLP follow up study TGLIA-1.039 conducted after the pivotal GLP study was summarized in a new subsection and specific findings were added to the table. The findings are supplementary information and did not change the conclusions drawn from the prior GLP and non-GLP toxicology studies. In addition, the finding "↓spleen weight" was moved within the table from Liver observations to Hematopoietic system observations.	Protocol section 1.3.3.3 Table 4 Summary of Nonclinical Observations and Clinical Risk Minimization Actions

NONSUBSTANTIAL (ADMINISTRATIVE) CHANGES

Description of Change	Affected Section(s) in Amended Protocol Version 6.0
Study title was updated to remove reference to healthy subjects. Protocol version and amendment number was updated.	Title page, protocol approval page, investigator agreement page, and synopsis
The telephone number for the CRO Clinical Research Contact, Trial Manager was removed to avoid future changes due to personnel changes. Information will be communicated by a different route. Medical monitor and sponsor contact remains.	Title page

Description of Change	Affected Section(s) in Amended Protocol Version 6.0
24-hour SAE reporting information was replaced with a new vendor fax number. On the title page reference is made to the SAE "form" rather than "worksheet" for consistency with section 8.6.6 Collection and Reporting of Serious Adverse Events.	Title page Protocol Section 8.6.6 Collection and Reporting of Serious Adverse Events
Clarification was added that the Safety Committee may include ad hoc members with relevant expertise, such as consultant with expertise in immune complex formation and serum sickness or with expertise in hepatology.	Synopsis, Safety Committee Protocol section 7.2 Safety Committee
For clarification "Predose – 4h" was removed. It was intended to denote the duration of constant monitoring but was less informative than the table footnote. The procedure was not changed.	Table 1 Schedule of Procedures, Part A and Table 2 Schedule of Procedures, Part B Pulse oximetry row
Minor editorial corrections were made to the table legends for clarification or to eliminate redundancy with the table information: Added to footnote #: "upon appearance of symptoms" Deleted from footnote ††: "at screening and Day 1" Deleted from footnote ♥: "on Day 1" Replaced in footnote ^^: "Day 30"by "the AE reporting period" Added to footnote ^^: "through the final follow up"	Legend to Table 1 Schedule of Procedures, Part A and Legend to Table 2 Schedule of Procedures, Part B
The abbreviation AT for aminotransferase was added.	IV List of Abbreviations
A clarification was added that all subjects who withdraw from the study prematurely during the investigational period (through Day 60 visit) will undergo all final in-clinic visit safety assessments as shown in Table 1. Schedule of Procedures, Part A and Table 2. Schedule of Procedures, Part B and footnote ***.	Protocol section 5.1.1 Handling of Withdrawals
Acknowledgement that an institutional SOP may be used if reviewed and approved by the sponsor was added. Some research institutions have their own policies for inventory and accountability	Protocol Section 6.2.3 Inventory and Accountability
"IRR" was added where it was missing from the phrase "symptoms of IRR or anaphylaxis/ anaphylactoid reaction"	Protocol section 7.3.2 Dosing Subjects Within A Dose Level (Within A Cohort)
To remove ambiguity and for consistency with the other study stopping rules where it was spelled out, the phrase "considered to be at least possibly related to TIMP-GLIA" was added to a study stopping rule. This does not represent a change to the rule, as this was already implied by context.	Synopsis, Study Stopping Rules Protocol section 7.3.6 Study Stopping Rules
Clarification was added that total volume infused should be recorded along with infusion start and stop time.	Protocol section 7.4 Treatment Compliance

Description of Change	Affected Section(s) in Amended Protocol Version 6.0
Clarification was added that cases of overdose should be reported to the sponsor as a "special situation" and any SAEs arising from overdose should be reported according to the specified procedures.	Protocol section 7.5 Emergency Procedures and Management of Overdose
Within the table of Clinical Laboratory Tests, the descriptive subtitle "Additional thrombotic/vascular markers" was added for the tests D-dimer, vWG, ICAM-1, fibrinogen, prothrombin fragment 1, 2, P-selectin.	Table 9 (was Table 11) Clinical Laboratory Tests
Cross reference to NCI CTCAE Version 4.0 (Published May 28, 2009 [v4.03: June 14, 2010]) or most current version was added in context of assessment of laboratory abnormalities as adverse events.	Section 8.6.1 Treatment Emergent Adverse Events
For emphasis, the description of Hy's Law or severe hepatic function abnormality in the absence of another etiology was duplicated from Appendix 13.1 Liver Safety Monitoring and Assessment (Drug Induced Liver Injury, DILI) in the protocol section defining SAEs and important medical events.	Protocol section 8.6.2 Serious Adverse Events
DILI case was called out to be reported to the medical monitor within 24 hours.	Protocol section 8.6.6 Collection and Reporting of Serious Adverse Events
Overdose, medication error, and pregnancy were defined as special situations to report to the sponsor. Note: Subsequent level 3 subsections were renumbered owing to this addition.	Protocol section 8.6.7 Collection and Reporting of Special Situations
Pregnancy outcome "congenital anomaly" description was revised for clarification. Reference is made to the SAE "form" rather than "worksheet" for consistency with section 8.6.6 Collection and Reporting of Serious Adverse Events.	Protocol section 8.6.9 (formerly 8.6.8) Pregnancy
For clarification, rationale for 30 minute and 35 minute post dose collection is provides and instruction to postpone the 35 minute collection to actual end of infusion if an infusion interruption >5 minutes occurs.	Protocol section 8.7.1 Blood Collection for PK
Clarification was made within Follow-up Procedures that liver abnormality information may be collected via a collective of appropriate CRFs not just one liver abnormality CRF (LA-CRF). Clarification was added that the last section refers to subject, not study, discontinuation. A statement was added that it could be in the subject's best interest to continue enrollment in the study to facilitate the additional testing and close medical observation to follow up a potential DILI. This is particularly relevant in a study with a single dose arm. Discontinuation of treatment would be considered separately from discontinuation from study.	Appendix 13.1 Liver Safety Monitoring and Assessment (Drug Induced Liver Injury, DILI)

13.10 Amendment 6: Summary of Changes to Protocol Version 7.0

The overall purpose of the amendment includes the following:

- Change to the composition of the Safety Committee to an independent Data Monitoring Committee
- Addition of the following safety laboratory tests
    - Cytokines via multiplex assay on Days 7 and 14 (Part A) and Days 14 and 21 (Part B)
    - Gliadin-specific T cell proliferation and cytokine secretion on Day 7 (Part A) Days 8 and 14 (Part B)
- Clarification to the cytokines reported as part of the multiplex assay
- Corrections to minor typographical errors

Effect on Consent Form:

For Part B of the study, the telephone visit at Day 21 has been changed to a clinic visit.

In most cases the site informed consent(s) for Parts A and B will NOT require a change because the language used to describe the tests above is not specific, nor does the volume of blood drawn over the course of the study change significantly. All sites are instructed to review their consent to ensure a change is not required.

Section	Change	Rationale
Throughout the synopsis and main body of the protocol.	Safety Committee changed to Data Monitoring Committee (DMC).	To create an independent review committee to review all safety data.
III. Synopsis, Study Design, Data Monitoring Committee 7.2 Data Monitoring Committee	Changed composition of DMC to: An independent DMC will be commissioned for this study. The DMC will be comprised of 3 physicians with expertise in immunology and/or vaccines clinical trials. A 4th physcician with expertise will serve as an advisor to the DMC, but in a non-voting capacity. Clarified role of medical monitor and other study team members with regard to interaction with DMC: The sponsor medical monitor will not be a member of the DMC. The sponsor medical monitor and other study team members will be available to answer questions of the DMC as	To ensure independence of DMC

Section	Change	Rationale
	necessary and during Open Sessions of the DMC. The medical monitor and other study team members will not participate in Close Sessions of the DMC.	
III. Synopsis, Endpoints, Safety and Tolerability IV. Schedule of Assessments, Table 1 and Table 2 3.2.1 3.2.1Safety and Tolerability Endpoints 8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety - Table 9 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction	Added pre and post-dose peripheral blood gliadin-specific T cell proliferation and cytokine secretion for subjects enrolled in the single dose groups ≥ 4 mg/kg in Part A (Day 7) and the for the repeat dose group in Part B (Day 14).	To determine whether TIMP-GLIA activates peripheral blood gliadin-specific T cells following dosing
III. Synopsis, Endpoints, Safety and Tolerability 8.5.6.5 Cytokines and Laboratory Tests to Follow-Up Suspected Anaphylaxis/Anaphylactoid Reaction	Added post-dose serum cytokine multiplex assay at Day for Part A (Day 7) and Part B (Days 14 and 21).	To determine whether TIMP-GLIA activates serum cytokines following dosing
III. Synopsis, Endpoints, Safety and Tolerability 8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety - Table 9	Clarified complete set of serum cytokines assayed in multiplex and additional cytokine assays: EGF, fractalkine, GM-CSF, GRO α, IFNα, IFN-γ, IL-1α, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, , IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, MIP1α, and MIP1β, TNF-α Clarified minimum serum cytokines to be used by DMC for dose escalation recommendation: IFN-γ, IL-1 β, IL-2, IL-2 soluble receptor, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IP-10, and TNF-α	Multiplex assay contained more cytokines than originally listed in protocol
8.8 Total Amount of Blood	Changed total blood volume in Part A is 307 mL and in Part B is 444 mL over 3 months (screening through Day 60).	

13.11 Amendment 7: Summary of Changes to Protocol Version 8.0

The overall purpose of the amendment includes the following:

- Instructions to manage mild to moderate infusion related reactions (IRR)
- Change to highest dose from 10 mg/kg to 10 mg/kg or a maximum of 750 mg

Effect on Consent Form:

The informed consent must be updated to include a change in the rate of infusion from 30 minutes to 2 -2.5 hours. The suggested wording is as follows:

"You will receive your dose by intravenous infusion over 2 or 2 ½ hours. Your health is being monitored continuously during the infusion. If you begin to develop signs of a reaction the infusion will be stopped for at least 5 minutes and the study doctor will determine if it is safe to proceed. If the infusion continues, the flow will be slowed and your dosing will take longer."

Section	Change	Rationale
III. Synopsis – Test Product; Dose; and Mode of Administration	**Added**: TIMP-GLIA: 0.1 mg/kg; 0.5 mg/kg, 1 mg/kg; 2 mg/kg; 4 mg/kg; 8 mg/kg; and 10 mg/kg **(up to 750 mg)**, administered by IV infusion.	To limit the amount of test product used subjects weighing more than 75 kg. This is not a safety issue. This is a clinical trial material inventory issue.
IV. Schedule of Assessments – Part A	**Added**: Predose **every 15 min during infusion,** ~~1h,~~ 2h, 4h, 8h, 12h, 24	To provide additional safety monitoring during the infusion
IV. Schedule of Assessments – Part A	**Added**: Predose (0hr), 30min, 35 min **(or end of infusion)**, 1h, 4h, 12h, 24h	To ensure a sample is obtained at the end of the infusion when rate is slowed.
IV. Schedule of Assessments – Part B	**Added for both Days 1 and 8**: Predose, **every 15 min during infusion,** ~~1h,~~ 2h, 4h, 8h, 12h, 24	To provide additional safety monitoring during the infusion
IV. Schedule of Assessments – Part B	**Added for both Days 1 and 8**: Predose (0hr), 30min, 35 min **(or end of infusion)**, 1h, 4h, 12h, 24h	To ensure a sample is obtained at the end of the infusion when rate is slowed.
2.5.3 TIMP-GLIA Maximum Recommended Starting Dose – Table 7: Planned Dose Levels	**Added:** Level 7 = 10.0 **or a maximum of 750 mg**	To limit the amount of test product used subjects weighing more than 75 kg. This is not a safety issue. This is a clinical trial material inventory issue.
7.4.1 Premature Termination of An Individual Subject's Infusion	**Added new ¶ 1**: If a subject develops signs and symptoms of IRR (dyspnea, generalized cutaneous reactions, tachypnea, hypoxia, tachycardia,	To provide for investigator instructions and discretion to restart the infusion should a subject so intial signs or symptoms of an IRR.

Section	Change	Rationale
	or if the subject experiences a decrease in blood pressure the investigator should stop the infusion for a minimum of 5 minutes or until signs and symptoms subside. Depending upon the severity of the signs and symptoms, and at the investigator and subject discretion, the infusion may be restarted as follows: - Restart the infusion at 25% of original rate for 15 minutes - If subject tolerates the reduced rate, increase to 50% of original rate for another 15 minutes, then increase to the original rate until infusion is complete	
7.4.1 Premature Termination of An Individual Subject's Infusion	**Modified ¶ 2**: Infusion will be **permanently discontinued** ~~terminated~~ if the subject develops clinical signs and symptoms of **Grade 3 or 4** IRR or anaphylaxis/ anaphylactoid reaction….	To provide more specificity to when an infusion must be discontinued.
7.4.2 Dosing Subjects Within A Dose Level (Within A Cohort) – Part A	**Modified ¶ 2**: Dosing additional subjects in a cohort will be stopped if 1 of the subjects at a dose level exhibits a dose-limiting toxicity (DLT) or should any subjects in the current dose cohort or any previously dosed subject (in any dose group) develop clinical signs and symptoms of **Grade 3 or 4** IRR or anaphylaxis/anaphylactoid reaction…	To provide more specificity of when an IRR or anaphylaxis/ anaphylactoid reaction results in the halting of dosing additional subjects within a cohort.
8.5.2 Vital Sign Measurements	**Modified ¶ 1**: Vital signs will be measured **every 15 minutes during the infusion and as otherwise** specified in the Schedules of Procedures for Part A (Table 1) and Part B (Table 2)**.**	To provide additional safety monitoring during the infusion

13.12 Amendment 8: Summary of Changes to Protocol Version 9.0

The overall purpose of the amendment includes the following:

- Specifying dose to be administered to subjects enrolled into Part B: 8 mg/kg up to a maximum of 650 mg
- Instructions for escalating rate of dose administration for subjects enrolled into Part B to minimize risk of infusion reaction
- Add collection of C3a and SC5B-9 complement levels at 15 and 30 minutes during infusion and at 24 hours following infusion for subjects enrolled in Part B to monitor for (sub-)clinical complement activation
- Clarify timing of pharmacokinetic sampling times

Effect on RISKS Section of the Consent Form for Part B:

The "Risk" Section of the Informed Consent for Part B should be updated as follows:

"TIMP-GLIA has been given as a single infusion to 17 subjects with celiac disease (Part A of this study). At the highest dose tested, approximately 650 mg, 2 of 4 subjects experienced a moderate infusion reaction. For one of the subjects the infusion was stopped and the signs and symptoms went away immediately. For the second subject, the infusion was stopped and the signs and symptoms went away immediately, and the infusion was restarted at a slower rate. The subject completed the infusion without any other problems.

Signs and symptoms of an infusion reaction to TIMP-GLIA include flushing (warm feeling or reddening of face, back and/or chest), rash, nausea, vomiting, back pain, low or high blood pressure, or increase in heart rate. These symptoms were mostly mild to moderate. All symptoms started within 2 minutes of the infusion starting and went away very quickly when the infusion was stopped or interrupted.

During studies in animals, some animals developed abnormalities in laboratory tests or in their tissues when TIMP-GLIA was given at doses higher than what is planned for this research study. Based on these animal studies it is is possible that TIMP-GLIA could cause an increase in the time it takes for your blood to coagulate, which may cause bleeding, or abnormal liver function tests. This could indicate that your liver may be harmed by TIMP-GLIA. Your blood tests may show that you have decreases in the numbers of white blood cells, platelets, and red blood cells and increases in the number of cells that turn into red blood cells ("reticulocytes"). This could indicate that your spleen and bone marrow may be harmed by TIMP-GLIA.

Since the TIMP-GLIA contains a gliadin extract, there is a possibility that you may experience worsening of your celiac disease symptoms (nausea, vomiting, bloating, diarrhea, abdominal pain, fatigue) after receiving the study medicine. TIMP-GLIA is designed to present gliadin in a noninflammatory way, but individual responses may vary.

All medications have a risk of an allergic reaction. Seek immediate medical help if you have any of the following signs of a serious allergic reaction: swelling of the face, mouth, lips, gums, tongue,

or neck. Other allergic reactions may include rash, hives, or blisters. Tell your study doctor as soon as possible if any of these reactions happen.

There may be other side effects of TIMP-GLIA that we don't know about. Tell your study doctor or study staff as soon as possible about all side effects that you have. If you are not honest about your side effects, it may not be safe for you to stay in the study."

Section	Change	Rationale
III. Synopsis – Exclusion Criteria #12	**Changed:** 12.The subject has a positive test result for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, methylenedioxymethamphetamine) or alcohol in urine – **except when the positive result arises from treatment under supervision of a medical doctor** - at Screening Visit or at Check-in.	Because medical cannabinoids are legal in many states and in this setting it would not be considered a drug of abuse – the intent of the exclusion criteria
III. Synopsis – Test Product; Dose; and Mode of Administration	**Changed**: **Part A:** TIMP-GLIA: 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg; 4 mg/kg; **and** 8 mg/kg~~; and 10 mg/kg~~ **~~(up to 750 mg)~~**, administered by IV infusion. **Part B: TIMP-GLIA: 8 mg/kg up to a maximum of 650 mg, administered by IV infusion.**	To specify the dose to be administered in Part B
III. Synopsis – Endpoints: Safety and Tolerability, ¶1	**Added:** Safety will be characterized by …immune complex detection by C1q binding **and by C3a and SC5B-9 (Part B only)**;…	To obtain complement levels during and after infusion to monitor for (sub-)clinical complement activation
IV. SCHEDULES OF ASSESSMENTS – Table 2. Schedule of Procedures, Part B	**Added:** **Collection of C3a and SC5B-9 at 15 and 30 minutes during each infusion and 24 hours after each infusion**	To monitor for (sub-)clinical complement activation
IV. SCHEDULES OF ASSESSMENTS – Table 2. Schedule of Procedures, Part B	**Changed:** Predose (0hr), 30min, ~~35min (or end of infusion),~~ 1h, **end of infusion,** 4h, 12h, 24h after each infusion	To reflect new dose rate

1.5 Benefit-Risk Assessment, ¶3 and 4	**Added:** **At the time of this amended protocol (Version 9), TIMP-GLIA has been given as a single infusion to 17 subjects with celiac disease (Part A of this study). At the highest dose tested, approximately 650 mg, 2 of 4 subjects experienced a moderate IRR. For one of the subjects the infusion was stopped and the signs and symptoms went away immediately. For the second subject, the infusion was stopped and the signs and symptoms went away immediately, and the infusion was restarted at a slower rate. The subject completed the infusion without any other problems.** **Signs and symptoms of IRR to TIMP-GLIA have included flushing (warm feeling or reddening of face, back and/or chest), rash, nausea, vomiting, back pain, low or high blood pressure, or increase in heart rate. These symptoms were either mild or moderate. All symptoms started within 2 minutes of the infusion starting and went away very quickly when the infusion was stopped or interrupted.**	To update risks based on results from Part A
2.5.3 TIMP-GLIA Maximum Recommended Starting Dose, Table 7 - Planned Dose Levels and Rationale	**Added:** Part A, Level 7; = 10.0 or a maximum of 750 mg - **Not administered;** CCI [redacted] **Changed:** Part B ~~To be determined~~ **8 mg/kg up to a maximum of 650 mg**	

3.2.1 Safety and Tolerability Endpoints, ¶1	**Added:** Safety will be characterized by… immune complex detection by C1q binding **and by C3a and SC5B-9 (Part B only)**, routine clinical laboratory….	To monitor for (sub-)clinical complement activation
4.2 – Exclusion Criteria #12	**Changed:** 12.The subject has a positive test result for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, cannabinoids, methylenedioxymethamphetamine) or alcohol in urine – **except when the positive result arises from treatment under supervision of a medical doctor** - at Screening Visit or at Check-in.	Because medical cannabinoids are legal in many states and in this setting it would not be considered a drug of abuse – the intent of the exclusion criteria
7.1 Dose and Regimen, ¶7	**Added:** **For Part B, TIMP-GLIA should 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**	To minimize risk of infusion reaction
8.5.6.1 Standard Clinical Laboratory Tests for Screening/Safety – Table 9	**Added** footnote **d** for when additional complement markers will be obtained	Clarification
8.5.6.5 C3a and SC5B-9 Complement Levels	**Added** new section **For Part B, C3a and SC5B-9 complement levels will be obtained during the infusion and 24 hours following the infusion (refer to Table 2. Schedule of Procedures, Part B).**	To monitor for (sub-)clinical complement activation

8.7.1 Blood Collection for PK, ¶2, 3, 4	**Deleted:** **S**~~cheduled blood collections for TIMP-GLIA measurement for pharmacokinetics are to occur at 30 minutes and at 35 minutes relative to start of infusion. The former represents the planned end-of-infusion collection. Because the clearance from the blood compartment is expected to be rapid, the latter blood collection facilitates the characterization of Tmax, even in the event of a brief unforseen procedural delays.~~ ~~In the event that the study drug infusion is interrupted (particularly > 5 minutes), the scheduled collection at 35 minutes post infusion start time should be postponed until the actual end-of-infusion. This should be documented in a similar manner as any other blood collection falling outside the defined window.~~ ~~The 30-minute collection should proceed relative to the infusion start time, with corresponding documentation that it does not represent the end-of-infusion. In addition, the volume of study drug administered at 30 minutes (as indicated by the infusion pump or estimated, as feasible) is to be recorded in the source.~~	To avoid confusion and refer back to Schedule of Assessments
8.8 Total Amount of Blood	**Changed**: The approximate total blood volume taken per CD subject in Part A is 307mL and in Part B is ~~444~~ **462** mL over 3 months (screening through Day 60).	Updated to reflect additional samples for complement levels
Appendix 13.3 Windows For PK Blood Sample Collection	**Changed:** Post dose **Part A** ≤ 35 minutes **Added**: **Post dose Part B – end of infusion - ± 6 minutes**	Clarify when 35 minute or end of infusion timepoint should be obtained

13.13 Amendment 9: Summary of Changes to Protocol Version 10.0

The overall purpose of the amendment includes the following:

- Expand Part B to include evaluation of 2 and 4 mg/kg dose levels in 2 subjects for each cohort, in addition to 2 subjects at the 8 mg/kg (up to a maximum of 650 mg) dose level
- Incorporate a 2+2 accelerated dose escalation model, in the event of a DLT in 1 subject in a cohort.

Effect on the Consent Form for Part B:

- Six to 12 subjects will be enrolled into Part B
- Part B will evaluate 3 dose levels of TIMP-GLIA: 2, 4, and 8 mg/kg up to a maximum of 650 mg. Two subjects will be enrolled into each dose group, beginning with 2 mg/kg.
- A safety committee will review the safety data when both subjects in a dose group have completed Study Day 3. If the committee thinks it is safe, the next group of 2 subjects will receive the next higher dose (e.g., 4 mg/kg).

Section	Change	Rationale
III. Synopsis – Study Design, Part B and 2.1 Overview of Study Design, Part B	**Changed:** ~~Part B~~ ~~At this point, the study will enter Part B. Eligible subjects (at least 3 CD subjects) will receive the maximum safe and tolerable dose of TIMP-GLIA identified from Part A. TIMP-GLIA will be administered as a single IV infusion, 7 days apart, on Day 1 and on Day 8. Each subject in Part B will be observed in clinic for 48 hours after each dose.~~ ~~At least 168 hours (7 days) will elapse after the second dose and safety confirmed before the next subject will be dosed. If dose-limiting toxicity occurs in 1 of the 3 subjects in Part B, the DMC may decide to increase enrollment by 3 subjects or to enroll another cohort of 3 subjects at a lower dose level. The DMC may recommend that up to a total of 12 subjects may be accrued to better define the relationship between dose and emerging safety signals.~~	Per FDA request to start at lower dose (2 mg/kg)

Section	Change	Rationale
	Part B Part B will evaluate 2 doses of TIMP-GLIA administered on Days 1 and 8. Two subjects will be enrolled into each of 3 cohorts at dose levels of 2, 4, and 8 mg/kg up to a maximum of 650 mg. Dose escalation will proceed only if Study Stopping Criteria ("Study Stopping Rules") are not met. If dose-limiting toxicity (DLT) occurs in 1 of the 2 subjects in a cohort, the DMC may decide to increase enrollment at the same dose level by 2 subjects. (2+2 design).	
III. Synopsis – Study Design, Data Monitoring Committee, ¶4, bullet 2 and 7.3 Data Monitoring Committee (Dose Levels ≥ 2 mg/kg), ¶3, bullet 2	**Changed:** - Expand the dose cohort to 4 subjects (accelerated titration 2+2, Part A **and Part B**) or to 6 subjects (standard 3+3, Part A ~~**and Part B**~~)	Per FDA request
III. Synopsis – Study Design, Data Monitoring Committee, ¶5 and 7.3 Data Monitoring Committee (Dose Levels ≥ 2 mg/kg), ¶5	**Changed:** **Additionally**, the DMC ~~will continue to monitor emerging safety data in Part B and~~ may meet ad hoc to determine if it remains acceptable to continue dosing.	For consistency with change to Part B
III. Synopsis – Selection of Study Population , ¶1 and 4 Study Population, ¶1	**Changed:** At least ~~22~~ **23** male and female subjects 18 to 75 years of age with….	Per FDA request
III. Synopsis – Test Product; Dose; and Mode of Administration, Part B	**Added:** **2, 4, and** 8 mg/kg up to a maximum of 650 mg, administered by IV infusion.	Per FDA request
IV. Schedules of Assessments, Table 2 - Schedule of Procedures, Part B	**Added:** C3a, **C5a**, and SC5B-9 complement level	C5a will be collected as part of the panel for complement – no additional blood required
1.5 Benefit-Risk Assessment, ¶1, Bullet 6	**Changed:** - **Part A** ~~of the FIH safety study~~ protocol TGLIA-5.001 uses a staggered dosing strategy across sites….	To differentiate from Part B

Section	Change	Rationale
1.5 Benefit-Risk Assessment, ¶1, Bullet 7	**Added:** - For Part B, subjects within a cohort may be enrolled/dosed concurrently.	To differentiate from Part A
1.5 Benefit-Risk Assessment, ¶1, Bullet 8	**Changed:** - ….. However, if 1 of the subjects at a dose level exhibits a dose-limiting toxicity, ~~an~~ additional ~~cohort~~ subject(s) will be dosed ~~in a staggered manner at~~ the same level to clarify ambiguous safety findings.	Corrected to reflect the actual addition of subject for toxicity.
1.5 Benefit-Risk Assessment, ¶1, Bullet 9	**Changed/Added:** - **In Part A**, when all subjects in a dose cohort complete procedures through 168 hours post dose, the overall safety and tolerability data (AEs, vital signs, 12-lead ECGs, clinical laboratory tests, cytokines) for the current cohort and available cumulative AE data from previous cohorts will be reviewed by the DMC who will determine the progression or termination of dosing. **In Part B, the DMC will review all safety date from a cohort when the last subject in a cohort has completed procedures through 48 hours.**	Part A remains the same. The 2 infusion reactions observed in Part A at 8 mg/kg occurred within minutes of the start of the infusion. Symptoms for both subjects resolved within an hour (maximum) of stopping the infusion. Forty-eight hours is a sufficient waiting period to observe an infusion reaction and its resolution.
1.5 Benefit-Risk Assessment, ¶1, Bullet 10	**Deleted**	Redundant to bullet 9
2.3 Rationale for the Trial Design, ¶1	**Changed and Added:** …. **In Part A**, an accelerated titration (2+2) model will be followed at the lowest doses followed by the standard 3+3 model at higher doses. (See also Figure 1. Schematic of Planned Dosing in Subjects With Celiac Disease, Part A and Part B and further description in Section 2.1, Overview of Study Design.) **In**	For clarity and FDA request

Section	Change	Rationale
	Part B, an accelerated titration (2+2) model will be followed.	
2.3Rationale for the Trial Design, ¶2	**Changed and Added:** ~~This~~ **In Part A**, **this design** ~~model~~ will allow the study proceed more quickly through the lowest doses at which little or no effect is anticipated to be observed…. **In Part B, the accelerated model allows the study to proceed at the lower doses at which little or no affect is expected.**	For clarity and at FDA request
2.3Rationale for the Trial Design, ¶5	**Changed:** Part B will be a repeat-dose study with ~~3~~ **2** subjects who will receive the first infusion on Day 1 and the second infusion on Day 8. ~~The dose selection for Part B will be based on the emerging safety and tolerability data from Part A as decided by the DMC.~~ If a dose-limiting toxicity occurs in 1 of the ~~3~~ **2** subjects in Part B, the DMC may decide to enroll an additional ~~3~~ **2** subjects at the same dose to confirm ambiguous safety or tolerability findings. ~~Depending upon the emerging safety data, they may also recommend enrollment of an additional cohort of 3 subjects at a lower dose to discern the safety profile of repeat dosing~~….	To reflect FDA request for design change to Part B
2.5.3 TIMP-GLIA Maximum Recommended Starting Dose, Table 7	**Added/Changed:** **Accelerated Titration 2 + 2** **Levels 1 – 3; 2, 4,** and 8 mg/kg up to a maximum of 650 mg ~~Safe & tolerable dose identified from Part A~~ **Maximum dose found to be safe and tolerable in Part A**	To reflect FDA request for design change to Part B
7.4.2 Dosing Subjects Within A Dose Level (Within A Cohort), Part B	**Changed:** During Part B (repeat dose), ~~1~~ subject**s** will receive 2 doses followed by in-clinic observation for at least 48 hours after each	To reflect FDA request for design change to Part B. The 2 infusion reactions observed in Part A at 8 mg/kg occurred within minutes of the start of the

Section	Change	Rationale
	dose. At least ~~168~~ **48** hours (~~7~~ **2** days) will elapse after the second dose and safety confirmed before ~~the~~ subjects in next subject higher dose cohort in Part B can be dosed. If dose-limiting toxicity occurs in 1 of the ~~3~~ **2** subjects in Part B, the DMC may decide to increase enrollment at the same dose level by ~~3~~ **2** subjects (n=~~6~~ **4**) ~~or to enroll another cohort of 3 subjects at a lower dose level. The DMC may recommend that up to a total of 12 subjects in a cohort may be accrued to better define the relationship between dose and emerging safety signals.~~	infusion. Symptoms for both subjects resolved within an hour (maximum) of stopping the infusion. Forty-eight hours is a sufficient waiting period to observe an infusion reaction and its resolution.
7.4.4 Dose Reduction	**Changed:** Depending upon emerging safety data, the DMC may recommend dosing a cohort of 2 subjects (accelerated titration 2 + 2, Part A **and Part B**) or 3 subjects (standard 3+3, Part A ~~and Part B~~) at a dose lower than the planned level to better identify the maximum tolerable dose of TIMP-GLIA.	For clarity
8.5.6 Laboratory Assessments, footnote d to Table 9	**Added:** d) For Part B, collect sample for C3a, **C5a**, and SC5B-9 complement levels at 15 and 30 minutes during infusion and at 24 hours following infusion.	C5a will be collected as part of the panel for complement – no additional blood required