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

NCT Number: NCT03738475

SAP Approve Date: May 14, 2019

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

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

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

Please note that the statistical output shells have been removed for brevity, since they are not a requirement of the statistical analysis plan.

STATISTICAL ANALYSIS PLAN (SAP)

Protocol Number:	TGLIA-5.002
Protocol Title:	A randomized, double-blind, placebo-controlled study of the safety, pharmacodynamics, efficacy, and pharmacokinetics of TIMP-GLIA in subjects with well-controlled celiac disease undergoing oral gluten challenge. (Version 2.0, December 10, 2018)
Product Name or Number:	TIMP-GLIA
Sponsor:	COUR Pharmaceuticals Development Company, Inc. 2215 Sanders Road Northbrook, IL 60062 USA
SAP Prepared by:	PPD
SAP Version Number (Date):	Version 1.0 (May 14, 2019)

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
C	Celsius
CI	confidence interval
CD	Celiac Disease
CSI-M	Celiac Symptom Index-Modified
CyTOF	mass cytometry
DGP-IgG	deamidated gliadin peptide immunoglobulin G
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot assay
GFD	gluten-free diet
IEL	intestinal intraepithelial lymphocyte
IFN-γ	interferon-gamma
IgA	immunoglobin A
IP	investigational product
IR	infusion reaction
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SFUs	spot forming units
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TIMP-GLIA	Tolerogenic Immune Modifying Particles-Gliadin
tTG-IgA	tissue transglutaminase immunoglobulin A
Vh:Cd	ratio of villus height to crypt depth
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

2 STUDY OVERVIEW

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

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

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

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

Blood is collected for analysis of gliadin-specific IFN-ɣ ELISpot, T cell proliferation, cytokine secretion, and gut-homing cells, pre-dose on Day 1, before starting the gluten challenge on Day 15, and Day 20 (6 days after first consumption of gluten).

Blood for PK (plasma gliadin concentrations) is collected on Day 8.

3 STUDY OBJECTIVES

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

The secondary objectives are:

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

4 GENERAL METHODS

4.1 Analysis Populations

Safety Population: The safety population includes all randomized subjects who receive at least one dose of study medication. Subjects will be analyzed according to the treatment actually received.

Pharmacokinetic Population: The PK population includes all randomized subjects who receive two doses of study medication and have at least one reported concentration. Subjects will be analyzed according to the treatment actually received.

Pharmacodynamic Population: The pharmacodynamic population includes all randomized subjects who receive two doses of study medication, complete at least the first 3 days of the gluten challenge (12 grams per day for 3 days), and have pharmacodynamic results on Study Days 1, 15, and 20.

Histology Population: The histology population includes all randomized subjects who receive two doses of study medication, complete the gluten challenge per protocol, and have both a baseline and Day 29 biopsy.

4.2 Summarization of Data

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

No imputation of values for missing data will be performed.

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

4.3 Sample Size Justification and Randomization

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

4.4 Statistical Output Production and Validation

All statistical analyses will be performed using SAS V 9.3 or higher (SAS Institute, Inc, Cary, North Carolina, USA). Validation and quality control of the tables and listings, which display the results of the statistical analysis of the data from this study will follow the appropriate CCI [redacted] standard operating procedures (SOPs).

5 SUBJECT DISPOSITION

The number of subjects who are treated, complete the study, and discontinue the study prematurely will be summarized by treatment group. Subject disposition information will also be displayed in a subject listing.

6 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

7 PROTOCOL DEVIATIONS

All major protocol deviations, as identified in the clinical database, will be presented in a subject listing.

8 MEDICAL AND SURGICAL HISTORY

Medical history items are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 21.1). The number and percent of subjects with past and current medical disorders at Study Day 1 will be presented by treatment group, system organ

class (SOC), and preferred term (PT). Medical history results will also be displayed in a subject listing.

9 PHYSICAL EXAM

A complete physical examination (PE) is done at Screening. Symptom-driven PEs are collected on Days 1, 8, 15, 20, 29, and 35. Any clinically significant findings are recorded on the AE form and reported as AEs. All findings will be displayed in subject listings.

10 PRIOR AND CONCOMITANT MEDICATIONS

Concomitant medications will be displayed by Anatomical Therapeutic Chemical (ATC) Class and Preferred Name using the most current World Health Organization (WHO) drug dictionary (Global B3 2018-09-01). The summaries will present the number and percentage of subjects using each medication by treatment group. Subjects who report more than one medication within the same ATC class or within the same preferred term will be counted only once within each level.

All prior and concomitant medications will be displayed in a subject listing.

11 DRUG EXPOSURE

Subjects receive an intravenous infusion on Days 1 and 8. The number and percent of subjects who receive one infusion or both infusions will be presented by treatment group. The total dose received (mL) will be listed. All findings will be displayed in subject listings.

12 PHARMACODYNAMIC ANALYSES

The pharmacodynamic endpoints are:

- IFN-ɣ SFUs in a gliadin-specific ELISpot
- Gliadin-specific T cell proliferation and cytokine secretion by ELISA
- Percentage of gut-homing cells by CyTOF

For all pharmacodynamic endpoints, “Baseline” will be Day 15 unless there is not enough blood to perform the assay, in which case the Baseline will be Day 1. All analyses of pharmacodynamic endpoints will be performed using the pharmacodynamic analysis population.

12.1 Interferon-Gamma Spot Forming Units

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values of IFN-γ SFUs at each time point. Summary statistics will also be presented for the change from baseline values to each post-baseline time point.

The mean changes from baseline in IFN-γ SFUs within treatment groups will be compared using a Wilcoxon Signed Rank Test. The null hypothesis to be tested is that there is no difference between mean values at baseline versus the post-baseline time point.

The mean changes from baseline in IFN-γ SFUs between treatment groups will be compared using a Wilcoxon Rank Sum Test. The null hypothesis to be tested is that there is no difference between mean change from baseline values for subjects treated with TIMP-GLIA versus subjects treated with placebo.

For each time point, frequencies and percentages will be presented for those subjects experiencing a 2-fold increase and/or an increase of at least 10 from baseline in IFN-γ SFUs (per 10^6 cells). The proportion of subjects with a 2-fold increase from baseline and an increase of at least 10 in IFN-γ SFUs (per 10^6 cells) in the placebo and TIMP-GLIA groups will be compared using a Fisher's Exact Test. The null hypothesis to be tested is that there is no difference between proportions for subjects treated with TIMP-GLIA versus subjects treated with placebo

All results will be displayed in a subject listing.

12.2 Gliadin-Specific T Cell Proliferation and Cytokine Secretion

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values of gliadin-specific T cell proliferation and cytokine secretion parameters (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IFN-γ, and TNF-α) at each time point. Summary statistics will also be presented for the change from baseline values to each post-baseline time point.

All parameters will be displayed in a subject listing.

12.3 CCI

CCI [redacted]

All results will be displayed in a subject listing.

13 HISTOLOGY ANALYSES

The histology endpoints are:

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

All analyses of histology endpoints will be performed using the histology analysis population.

All biopsy results will be displayed in a subject listing.

13.1 Ratio of Villus Height to Crypt Depth

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the villus height to crypt depth ratio (Vh:Cd) at each time point. Summary statistics will also be presented for the change from baseline values to each post-baseline time point.

The mean changes from baseline Vh:Cd within treatment groups will be compared using a Wilcoxon Signed Rank Test. The null hypothesis to be tested is that there is no difference between mean values at baseline versus the post-baseline time point.

The mean changes from baseline in Vh:Cd between treatment groups will be compared using a Wilcoxon Rank Sum Test. The null hypothesis to be tested is that there is no difference between mean change from baseline values for subjects treated with TIMP-GLIA versus subjects treated with placebo.

Frequencies and percentages will be presented for those subjects with a decrease of at least 0.4 from baseline in Vh:Cd on Day 29. The proportion of subjects with a decrease of ≥ 0.4 in Vh:Cd in the placebo and TIMP-GLIA groups will be compared using a Fisher's Exact Test. The null hypothesis to be tested is that there is no difference between proportions for subjects treated with TIMP-GLIA versus subjects treated with placebo.

In these displays, baseline is defined as the values that are obtained during the Screening period.

13.2 Intestinal Intraepithelial Lymphocytes

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values of IELs at each time point. Summary statistics will also be presented for the change from baseline values to each post-baseline time point.

The mean changes from baseline in IELs within treatment groups will be compared using a Wilcoxon Signed Rank Test. The null hypothesis to be tested is that there is no difference between mean values at baseline versus the post-baseline time point.

The mean changes from baseline in IELs between treatment groups will be compared using a Wilcoxon Rank Sum Test. The null hypothesis to be tested is that there is no difference between mean change from baseline values for subjects treated with TIMP-GLIA versus subjects treated with placebo.

In these displays, baseline is defined as the values that are obtained during the Screening period.

14 CELIAC DISEASE SIGNS AND SYMPTOMS

Subject responses to the CSI-M will be summarized using descriptive statistics and displayed in a subject listing.

15 SAFETY ANALYSES

15.1 Adverse Events

All AEs will be coded using the MedDRA coding system (version 21.1). Frequency tables will be presented by treatment group for all AEs and SAEs by SOC and PT. Frequency tables will also be produced by treatment group for AEs leading to discontinuation from IP, by severity, and by causality. Additionally, AEs associated with an infusion reaction will be tabulated. No formal statistical testing will be done.

Subjects who have the same AE occur more than once will be counted only once for that event. Subjects who have more than one AE within a system organ class will be counted only once in that system organ class.

Subject listings of all AEs will be provided.

15.2 Laboratory Tests (Hematology, Serum Chemistry)

For quantitative data, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment group. Summary statistics will also be presented for the change from baseline values to each post-baseline time point. Frequency tables of laboratory abnormalities by grade and treatment group will be provided.

In these displays, baseline is defined as the values that are obtained immediately pre-dose on Day 1.

Clinically significant laboratory abnormalities are recorded on the AE form and reported as AEs.

All laboratory results, including screening laboratory results, will be displayed in subject listings.

15.3 Vital Signs

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values for temperature, systolic and diastolic blood pressure, and heart rate at each time point by treatment group. Summary statistics will also be presented for the change from baseline values to each post-baseline time point.

In these displays, baseline is defined as the values that are obtained immediately pre-dose on Day 1.

All vital sign results will be displayed in a subject listing.

15.4 Electrocardiograms

Electrocardiograms (ECGs) are performed at Screening only. All ECG results will be displayed in a subject listing.

15.5 Serum Cytokines

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for the observed values of cytokines (IL-1 β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, IFN-γ, TNF-α) by treatment group for the safety population. Summary statistics will also be presented for the change from baseline values to each post-baseline time point. In these displays, baseline is defined as the values that are obtained immediately pre-dose on Day 1.

All results will be displayed in subject listings.

15.6 Celiac Serology, Anti-Drug Antibody and Immune Complexes

IgA, tTG-IgA are collected only at Screening. The results will be displayed in a subject listing.

15.7 Anti-Drug Antibody and Complement Levels

Summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for DGP-IgG (anti-drug antibody), C1q binding, and C3a, C5a and SC5B-9 complement levels for the observed values by treatment group for the safety population. Summary statistics will also be presented for the change from baseline values to each post-baseline time point, where applicable. In these displays, baseline is defined as the values that are obtained immediately pre-dose on Day 1.

All results will be displayed in subject listings.

16 PHARMACOKINETIC ANALYSES

Individual subject plasma gliadin concentrations will be summarized by nominal collection time using descriptive statistics for patients in the PK population. Further analysis may be performed as deemed necessary for the interpretation of the data and will not be reported in the clinical study report.

All results will be displayed in subject listings.

17 SUBJECT LISTINGS

Data that are collected and entered into the study database but that are not displayed in the summary tables specified in the preceding sections will be presented in subject listings.

18 INTERIM ANALYSES

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

19 FINAL SIGN-OFF FOR COUR PHARMACEUTICALS DEVELOPMENT COMPANY, PROTOCOL TGLIA-5.002 STATISTICAL ANALYSIS PLAN

PPD

May 17, 2019

Date

May 17, 2019

Date

20 REVISIONS TO STATISTICAL ANALYSIS PLAN

Date	Revision	Statistician's Signature
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