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

SAP Approve Date: October 9, 2018

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 AND PHARMACOKINETIC ANALYSIS PLAN (SAP)

Protocol Number:	TGLIA-5.001
Protocol Title:	A Phase I, 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 (version 10.1, September 13, 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 2.0 (October 9, 2018)

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
E	d
W	K
A	A h
A 0-h	h h
A 0-t	h
A 0-u	A d g h
A 0-fi	h h
Ab p	M
M	h
C	C
C	T
C h	h
C m	P
D	T
C	F
C h	L h g
R	R
M	M
G	h
H	-in -h
D	-d
h	N
M	M
N	m
K	h
P	h
R	M
R e	h
S	i
S	h
D	d

Abbreviation or Term	Definition
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
T_{lag}	[illegible]
T_{max}	[illegible]
λ_z	[illegible]
$t_{1/2}$	[illegible]
V_s	[illegible]
[illegible]	[illegible]

2 STUDY OVERVIEW

Table 1: Planned Dose Levels and Rationale

		Single Dose mg/kg	Rationale
	Part A		
	Part B	**Repeat dose mg/kg**	
			A.

Stopping Criteria ("Study Stopping Rules")

Schedules of Procedures

3 STUDY OBJECTIVES

The primary objective was 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.

The secondary objectives were:

- 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.

4 GENERAL METHODS

4.1 Analysis Populations

Safety Population: The safety population was defined as all subjects who sign the study-specific informed consent documents and received at least one dose of study medication.

Pharmacokinetic Population: The PK concentration population was defined as all subjects who received at least one dose of study drug (and time of dosing is known) and had at least 1 drug concentration measurement. The PK parameter population was defined as all subjects who received at least one dose of study drug and had at least 1 PK parameter reported.

Inclusion of subjects in the PK analysis datasets (PKAD) with missing data or protocol deviations was considered by the pharmacokineticist on a case-by-case basis.

4.2 Summarization of Data

Study results were summarized by Part A and Part B and by treatment (dose) group unless otherwise specified.

No imputation of missing data was performed. No windowing of visits was performed unless otherwise specified.

4.3 Sample Size Justification and Randomization

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

4.4 Statistical Output Production and Validation

All statistical analyses were 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, followed the appropriate CCI [redacted] standard operating procedures (SOPs).

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[illegible]

α, fractalkine, INF-α, INF-γ, IL
1α, IL-1β, IL L - 10, MIP1α, MIP1β, TNF-α.

[illegible]

12 [illegible]

[illegible]

γ, IL-1β, TNF-α, IL[illegible]

[illegible]

3 P[illegible]

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- [illegible] λ_z [illegible]
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- No value for λ_z [illegible] be reported for cases where a valid estimate of λ_z [illegible]
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3 PK Parameters and Definitions

PK Parameter	Definition	Calculation Method
C_{max}		
T_{max}		
C_{last}		
T_{last}		
AUC_{0-last}		
AUC_{0-t}		
AUC_{0-tau}		
AUC_{0-inf}		$AUC_{0-last} + C_{last}/\lambda_z$
$AUC_{\%Extrap}$		$AUC_{0-inf} - AUC_{0-last}$ / AUC_{0-inf}
λ_z		
$t_{1/2}$		$\ln(2)/\lambda_z$
CL		$Dose/AUC_{0-inf}$ or $Dose/AUC_{0-tau}$
V_s		$Dose/AUC_{0-inf}$
R_{ac}		AUC_{0-inf} / AUC_{0-inf}
C_{max} D		C_{max} / Dose
AUC_{0-last} D		AUC_{0-last} / Dose
AUC_{0-inf} D		AUC_{0-inf} / Dose

An independent DMC was commissioned for this study for dose levels ≥ 2 mg/kg. The DMC

17 FINAL SIGN-OFF FOR COUR PHARMACEUTICALS DEVELOPMENT COMPANY, PROTOCOL TGLIA-5.001 STATISTICAL ANALYSIS PLAN

PPD

Oct 9, 2018

Date

Oct 9, 2018

Date

Oct 9, 2018

Date

[redacted]

[redacted]	[redacted]	Statistician's Signature
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