FINAL CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 1, Double-Blind, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TRL345 in Healthy Volunteers
Study Number:	TRL345-102
Study Phase:	Phase 1
Test Product:	TRL345
IND Number:	125858
Indication:	Healthy Volunteers
Sponsor:	Trellis Bioscience, Inc. 702 Marshall St., Suite 301 Redwood City, CA 94063
Medical Monitor:	Anton Leighton, MD Chief Medical Officer Trellis Bioscience, Inc. Phone: (510) 385-7273 Email: tony@antonleighton.com

Version	**Date**
Original Protocol, v1.0	08 March 2023

SPONSOR SIGNATURE PAGE

TRL345-102

Study Title: A Phase 1, Double-Blind, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TRL345 in Healthy Volunteers

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

Signed: DocuSigned by: Anton Leighton 70FBB6E4915C4DF... 3/8/2023

Anton Leighton, MD
Chief Medical Officer
Trellis Bioscience, Inc.

Date

Signed: DocuSigned by: Stefan Ryser CB6C7CAF805F47B... 3/8/2023

Stefan Ryser, PhD
Chief Executive Officer
Trellis Bioscience, Inc.

Date

INVESTIGATOR SIGNATURE PAGE

TRL345-102

Study Title: A Phase 1, Double-Blind, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TRL345 in Healthy Volunteers

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

Signed: _____ _____

Name
Title
Institution or Company

Date

Signed: _____ _____

Name
Title
Institution or Company

Date

STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Applicable Federal, State, and Local Regulations and Guidance

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADA	Anti-drug antibody
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CMO	Chief Medical Officer
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
DG	Dose group
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
CFR	Code of Federal Regulations
GLP	Good Laboratory Practice
HBsAG	Hepatitis B surface antigen
HCMV	Human Cytomegalovirus
HCT	Hematopoietic Cell Transplant
HCV	Hepatitis C virus
HIG	Hyperimmune globulin
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICH-GCP	International Conference of Harmonisation-Good Clinical Practice

Abbreviation	Definition
IL-1α	Interleukin-1alpha
IR	Infusion reaction
IRB	Institutional Review Board
IV	Intravenous, intravenously
IUD	Intrauterine device
IP	Investigational Product
LDH	Lactic acid dehydrogenase
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
NOAEL	No observed adverse effect level
Nt-proBNP	N-terminal pro-B-type natriuretic peptide
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID	Severe Combined Immune Deficiency
SD	Standard deviation
SMC	Safety Monitoring Committee
SOC	System organ class
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

SYNOPSIS

<table>
<tr><td colspan="2">Sponsor: Trellis Bioscience, Inc.</td></tr>
<tr><td colspan="2">Study Title: A Phase 1, Double-Blind, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of TRL345 in Healthy Volunteers</td></tr>
<tr><td colspan="2">Test Product: TRL345</td></tr>
<tr><td colspan="2">Name of Active Ingredients: TRL345 – Anti-Human Cytomegalovirus (HCMV) IgG1κ Human Monoclonal Antibody</td></tr>
<tr><td>Study Number: TRL345-102</td><td>Study Phase: Phase 1</td></tr>
<tr><td colspan="2">Primary Objective:
Assess the safety and tolerability of TRL345 when administered intravenously (IV) as a single dose in healthy adult volunteers
Secondary Objectives:
Characterize the pharmacokinetics (PK) of a single IV infusion of TRL345 overall and by DG
Assess the immunogenicity of TRL345 as measured by anti-drug antibodies (ADAs)
Exploratory Objectives:
Explore the pharmacodynamics (PD) of TRL345 in an ex vivo study using serum samples to explore the capacity of various concentrations of TRL345 to neutralize HCMV in human serum
Explore if there are any differences in adverse events, clinical labs, or PK across dose groups to explore if there are any signs of off-target binding of TRL345</td></tr>
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Study Design

This is a Phase 1, first-in-human, double-blind, single ascending dose study to assess the safety, PK, PD, and preliminary activity of TRL345. Healthy subjects aged 18-65, inclusive, will be screened.

Subjects who meet all inclusion and no exclusion criteria, will be enrolled into the study, assigned to a dose group (DG), and randomized to receive TRL345 or placebo. Each DG will include 8 subjects; 6 will receive TRL345 and 2 will receive placebo. An established ELISA assay available in commercial laboratories to detect IgG antibodies against CMV will be used to determine serostatus of subjects prior to randomization. Dosing of the first two subjects (one randomized to TRL345 and one randomized to placebo) in each DG will be done on the same day. Dosing of the other subjects will occur at least 72 hours after the first two subjects have been dosed and following review of the blinded safety data from the first two subjects in the DG by the PI and Sponsor. After all subjects within a DG have completed Day 15, a Safety Monitoring Committee (SMC) will review all available safety data through Day 15 prior to making a recommendation regarding escalation to the next higher DG.

Subjects will be admitted to a Phase 1 research unit prior to the IV administration of a single dose of IP. In order to maintain the blind, subjects will be dosed as follows: DG1 will receive 1 mg/kg of TRL345 or 0.1mL/kg of placebo and DG2 will receive 10 mg/kg of TRL345 or 1mL/kg of placebo. All subjects (randomized to either TRL345 or placebo) will receive IP infused over 60 minutes.

Subjects will be closely monitored for AEs and SAEs, including infusion reactions (IRs), from the onset of the infusion through discharge from the Phase 1 research unit. Subjects will be assessed for safety and tolerability, including AEs and SAEs, at each follow-up visit after discharge through Day 76. A physical exam, vital signs, and routine clinical lab tests (chemistry and hematology) will be done on Days 1, 2, 3, 8, 15, 29, and 43. An ECG will be done on Days 1 and 8.

Serum for PK will be collected on Days 1 (0, 1, 2, 4, 6, 12 hours after start of infusion), 2 (24 hours after start of infusion) and 3 (48 hours after start of infusion), and on Days 8, 15, 29, 43 and 76. Additionally, serum samples will be taken on Days 1, 8, 29, 43 and 76 for measurement of anti-TRL345 antibody levels. Samples taken on Days 1, 43, and 76 will be analyzed using an electrochemiluminescence assay. Samples collected on Days 8 and 29 will be held for exploratory analysis, if warranted, based on Day 43 and Day 76 ADA analysis results. The proportion of subjects with detectable anti-TRL345 antibody responses prior to dosing and IP-emergent anti-TRL345 antibodies will be reported.

Additional serum samples will be collected on Days 1 (pre-infusion and 1 hour after start of infusion), 15, 29, 43, and 76 for *ex vivo* PD assessments, which will be conducted at Professor McVoy's lab as defined in a separate protocol, whereby the dosed participants of the study will remain anonymous.

Additional serum samples will also be obtained on Days 1 (pre-infusion), 3, 8, 15, 29, and 43 for possible additional exploratory analyses that may be necessary to further explore any unexpected safety or tolerability observations.

Number of Subjects Planned: 16; 8 subjects will be randomized 6:2 (TRL345:placebo) to a DG (1 and 10 mg/kg doses)

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

1. Healthy male and non-pregnant, non-breast-feeding female subjects at between 18 and 65 years of age, inclusive, and representative of the general population
2. Willing and able to provide written informed consent.
3. Availability for the entire duration of the study, and willingness to adhere to protocol requirements
4. In good health, as determined by lack of clinically significant abnormalities in health assessments performed at the Screening Visit, as judged by the Principal Investigator (PI) or as delegated by the PI to a physician or nurse practitioner as sub-investigator.
5. Men and women of childbearing potential (WOCBP) must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, or intrauterine device (IUD) for 28 days before Screening and through Day 76. Men must also refrain from donating sperm from Day 1 through Day 76.

Exclusion Criteria

1. Inability to tolerate blood draws or has poor venous access
2. Body mass index (BMI) <18.5 or ≥35 kg/m^2
3. Clinically significant vital sign abnormalities (systolic blood pressure lower than 90 or over 160 mmHg; diastolic blood pressure lower than 50 or over 100 mmHg; or, heart rate less than 45 or over 100 bpm) at the Screening Visit
4. ECG with clinically significant findings, including:
    a. Conduction disturbance (complete left or complete right bundle branch block or nonspecific intraventricular conduction disturbance with QRS ≥120 msec, PR interval ≥220 msec, any second- or third-degree atrioventricular block, or prolongation of the QT interval corrected according to Fridericia's correction [>450 msec male and >460 msec female])
    b. Significant repolarization (ST-segment or T-wave) abnormality; or
    c. Significant atrial or ventricular arrhythmia; or
    d. Frequent atrial or ventricular ectopy (e.g., frequent premature atrial contractions, 2 premature ventricular contractions in a row); or
    e. ST-elevation consistent with ischemia or evidence of past or evolving myocardial infarction.

5. Presence of any gastrointestinal pathology (e.g., chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g., diarrhea, vomiting), or progressive liver or kidney disease
6. Diagnosis of diabetes mellitus
7. History of acute or chronic pancreatitis or upper right quadrant postprandial discomfort or pain within the last 2 years
8. Clinically relevant medical conditions that, in the opinion of the PI, may interfere with the evaluation of the trial drug, e.g., progressive cardiovascular disease
9. Concurrent acute or chronic infections (e.g., viral infections, except chronic recurrent herpes simplex infections)
10. Significant abnormal safety labs, defined as:
    - Greater than 30% outside of the normal range for any of the following: hemoglobin, white blood cell (WBC) count, platelet count, neutrophil count and blood urea nitrogen
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), direct bilirubin or indirect bilirubin >2 × the upper limit of normal
    - Activated partial thromboplastin time (aPTT) prolongation >1.5 x ULN
    - Hemoglobin A1C (HbA1C) >5.6%
    - Fasting glucose level of ≥100 mg/dl (5.6 mmol/L)
    - Renal function based on the, i.e., estimated creatinine clearance < 70 mL/min (Cockcroft-Gault formula using ideal body weight)
    - Hemoglobin ≤ 128 g/L (males) and ≤ 115 g/L (females), and hematocrit ≤ 37% (males) and ≤ 32.0% for females
11. Positive test results for HIV, Hepatitis B (HBsAg), or Hepatitis C (HCV) at the Screening Visit
12. History of significant drug abuse within one year prior to the Screening Visit and/or ongoing
13. History of significant alcohol abuse within one year prior to the Screening Visit defined as more than fourteen units of alcohol per week [one “unit” is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits)
14. Positive test for drugs of abuse, ETOH and nicotine (cotinine) at the Screening Visit
15. Positive serum beta-human chorionic gonadotropin test for pregnancy, pregnant, or nursing women
16. Unwilling to refrain from donating blood or plasma during the study.
17. Use of any new prescription medication or over-the-counter (OTC) product (including natural food supplements, vitamins, herbs) within 14 days prior to dosing

18. Receipt of any vaccine or booster within 14 days prior to Day 1 or planned vaccination or booster within 4 weeks after IP administration
19. Any planned medical intervention or personal event that might interfere with the ability to comply with the study requirements
20. Is current study site staff paid entirely or partially by the contract for this trial, or staff who are supervised by the PI or sub-PI
21. Receipt of an investigational product, or participation in another trial involving a marketed or investigational drug within 30 days of Day 1, or 5 half-lives of the investigational drug, whichever is longer
22. Any other comorbidity or condition that, in the opinion of the Investigator would make the subject unsuitable for the study or unable to comply with the study requirements

Duration of Treatment: 1 dose. The total duration of the study is 76 days (approximately 11 weeks).

Test Product; Dose; and Mode of Administration: TRL345 administered by IV infusion.

- Dose level 1: 1 mg/kg
- Dose level 2: 10 mg/kg

Reference Therapy; Dose; and Mode of Administration: Normal saline, administered by IV infusion. To protect the blind, DG1 will receive 0.1 mL/kg and DG2 will receive 1 mL/kg.

Safety Monitoring:

Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will review safety, dose escalation, and overall timelines. The SMC will review SAEs (Section 7.2.2) and ≥ Grade 3 AEs that are "Likely" (Section 7.2.3) to be related to TRL345. Any infusion-related adverse event will be reported to the SMC within 24 hours. All data will be reviewed in an unblinded fashion upon completion of each DG.

Dose Escalation

The SMC will review all available safety data after the last subject in a DG has completed Day 15. They will evaluate the AEs, vital signs, and available laboratory results in the context of the established Study Pausing Rules (see below).

If Study Pausing Criteria are not met, the SMC will make one of the following recommendations:

- Escalate to the next higher dose as planned
- Expand the DG to obtain additional safety information based on possible trends in laboratory assessments or Grade 1 (Mild) adverse events

Study Pausing Rules

Should any one of the following criteria occur, the Sponsor will stop study recruitment and will not administer IP to any subject until the SMC has reviewed all available study data:

- First occurrence of an AE with severity Grade 3 (Severe) or Grade 4 (Potentially Life Threatening) considered to be at least likely related to TRL345
- 2 or more subjects with an AE of severity Grade 2 (Moderate) in the same body class considered to be at least likely related to TRL345 (among total number of subjects dosed)
- Any other toxicity which in the opinion of the SMC precludes further dosing.

Following review of safety data, the SMC will make a recommendation to continue the study as planned, to modify, or to terminate the study.

Criteria for Evaluation:

Safety:

- Incidence and severity of AEs (includes vital signs, ECGs, laboratory evaluations, and physical examination findings)
- Incidence of SAEs

PK: Serum concentrations of TRL345 will be determined by ELISA

Immunogenicity: Incidence of baseline and IP-emergent ADA (i.e., anti-TRL345 antibodies) in serum will determined by electrochemiluminescence assay

PD: Serum samples will be taken to explore the capacity of various concentrations of TRL345 to neutralize CMV in *ex vivo* assessments

Statistical Methods

Sample Size: No formal sample size calculations were performed. The numbers of subjects per DG are typical for Phase 1 studies in healthy adult volunteers.

Analyses:

Safety: Frequencies and percentages of subjects with AEs and SAEs will be summarized by dose group. Vital signs, ECGs, laboratory evaluations, and physical examination findings will be summarized with descriptive statistics by dose group. Additional serum samples will be taken and stored for possible exploratory analyses that may be necessary to further explore any unexpected safety or tolerability observations.

PK: Individual subject TRL345 serum concentrations and derived PK parameters will be summarized using descriptive statistics.

Immunogenicity: Anti-TRL345 antibodies will be summarized with descriptive statistics by DG.

PD: Serum samples will be taken and evaluated for *ex vivo* PD assessments.

SCHEDULE OF EVENTS

Study Day	**Screening**	**1**	**2**	**3**	**8**	**15**	**29**	**43**	**76**
Study Week					1	2	4	6	11
Window (days)	−8 (+/−6)	− 1	0	0	± 1	± 3	± 3	± 3	± 5
Visit Type	A	RU	RU	RU	A	A	A	A	A
Procedure									
Informed Consent	X								
Eligibility	X	X[1]							
Demographics	X								
Medical/Disease History	X								
Complete Physical Exam	X								
Targeted Physical Exam		X[1]	X	X	X	X	X	X	
Vital Signs[2]	X	X[3]	X	X	X	X	X	X	
Weight	X	X[1]						X	
Height	X								
12-Lead ECG in triplicate[4]	X	X			X				
Laboratory Tests									
Serum Chemistry[5]	X	X[1]	X	X	X	X	X	X	
Hematology	X	X[1]	X	X	X	X	X	X	
Amylase, lipase, creatine kinase[6]		X[1]		X	X	X			
Fasting glucose	X	X[1]		X	X	X	X	X	
HbA1C	X								
Fasting blood insulin level		X[1]		X	X	X	X	X	
Additional serum sample for possible exploratory analyses[7]		X[1]		X	X	X	X	X	
NT-proBNP, IL-1α		X[1]		X		X	X	X	
CMV Serology[8]	X								
Serum Pregnancy Test (WOCBP)	X							X	
HIV, Hepatitis B, C Serology	X								
Urine Drug Test	X								
Randomization		X[1]							
Dosing of IP (TRL345 or placebo)		X							
PK sampling – serum[9]		X	X	X	X	X	X	X	X
PD sampling – serum[10]		X				X	X	X	X
ADA sampling – serum[11]		X[1]			X		X	X	X
Adverse Events		X	X	X	X	X	X	X	X
Concomitant Medications		X[1]	X	X	X	X	X	X	X
Overall Status								X	X

Visit Type: A = ambulant, RU = Research Unit, NA = phone call

1. To be performed prior to the administration of IP.
2. Vital signs include temperature, blood pressure, and heart rate. Vital signs should be obtained after subject is resting for 5 minutes. The window for all vital signs is ± 10 minutes.
3. On Day 1, vital signs will be obtained within 60 minutes prior to dosing, at 15, 30, and 60 minutes (end of the infusion), and 1 hour and 4 hours after the end of the infusion.

4. Subjects may not use tobacco or nicotine within 4 hours prior to the ECG. ECG on Day 1 will be performed within 4 hours after completion of the infusion.
5. Serum chemistry at Days 1, 15, and 29 is to include hsCRP and LDH.
6. Subjects must refrain from strenuous exercise within 5 days prior to assessment of creatine kinase
7. An additional 5 mL serum sample will be collected immediately prior to the IP infusion on Day 1 and on Days 3, 8, 15, 29, and 43 and stored for possible exploratory analyses.
8. An established ELISA assay available in commercial laboratories to detect IgG antibodies against CMV will be used to determine serostatus of subjects.
9. Samples for PK will be collected immediately prior to the IP infusion on Day 1 and end of the infusion (60 minutes) ± 15 minutes, and hours 2 ± 15 minutes, 4 ± 15 minutes, 6 ± 15 minutes, 12 ± 1 hour, 24 (Day 2) ± 1 hour, and 48 (Day 3) ± 1 hour after start of infusion and then on Days 8, 15, 29, 43, and 76.
10. Samples for PD will be collected immediately prior to the IP infusion on Day 1 and end of the infusion (60 minutes) ± 15 minutes and on Days 15, 29, 43, and 76 for *ex vivo* PD assessments.
11. Samples for ADA will be collected immediately prior to the IP infusion on Day 1 and on Days 8, 29, 43, and 76. ADA samples collected on Days 8 and 29 will be held for exploratory analysis, if warranted.

1 INTRODUCTION

1.1 Background

Human Cytomegalovirus (HCMV) infection is widespread and can result in severe sequelae in susceptible populations. HCMV can infect a diverse number of cells resulting in productive viral replication in epithelial, endothelial, fibroblasts, hepatocytes, muscle and neuronal cells. Following primary infection, HCMV finds its way to the hematopoietic progenitor cells in the bone marrow where it enters a life-long latency. Sporadic reactivation from latency is believed to be frequent [Struble 2021].

Antibody therapy of HCMV provides an alternative to antiviral drugs with an expectation of qualitatively lower toxicity. The leading small molecule antiviral effective against HCMV, ganciclovir (and its oral prodrug formulation valganciclovir), has side effects (including neutropenia, nephrotoxicity, and potential mutagenicity) that make its use problematic for major indications, including congenital transmission or the early post-transplant period for HCT [Kalil 2009]. Although the recently approved small molecule antiviral letermovir has reduced neutropenic activity and is therefore useful in HCT, it has not eliminated CMV reactivation in adult HCT patients [Marty 2020].

Antibodies against HCMV gB have long been known to neutralize virus infection in both fibroblasts and epithelial cells [Meyer 1992]. Antibodies recognizing antigenic determinant (AD)-2 site I on gB mainly mediate this effect [Baraniak 2018]. Although the AD-2 linear epitope region is highly conserved among clinical isolates of the HCMV, different antibodies against this epitope have different ultra-fine specificity for the epitope [Lantto 2003; Ohlin 1993; Silvestri 1993]. Of the mAbs cloned by Trellis, TRL345 had the best potency *in vitro***,** substantially higher than a well-known human mAb ITC-88 [McCutcheon 2014]. Antibodies with the specificity of TRL345 are present in CMV-HIG, but only at a level of ~1-2% determined by antigen ELISA.

Vaccines are also in development, but face formidable challenges including adeptness of HCMV in evading the immune system and limited animal models [Inoue 2018]. A recombinant gB formulated with MF59 adjuvant elicited strong humoral responses and was 50% effective in preventing primary infections in solid organ transplant infants, but with limited durability [Cui 2019].

1.2 TRL345

TRL345 is a human IgG1kappa (G1m1,17 (z,a); Km3 allotype) monoclonal antibody cloned from human B lymphocytes which targets the highly conserved AD-2, Site I epitope on the gB viral glycoprotein of the Human Cytomegalovirus (HCMV). The short name throughout this document is TRL345. The formal identifying name for TRL345 drug product is TRL345 for intravenous (IV) injection. TRL345 for IV injection is supplied at a nominal concentration of 10 mg/mL in single-

use vials. Each vial contains 10 mL of TRL345 in 20 mM histidine/150 mM sodium chloride/pH 6.0. TRL345 for IV injection is a sterile, clear, colorless, preservative-free liquid concentrate for IV infusion. TRL345 IV will be infused in subjects without further dilution.

The biological activity of TRL345 was characterized by a series of in vitro assays. First, it was found that TRL345 neutralized 15 out of 15 HCMV clinical isolates spanning the viral phylogeny, consistent with the highly conserved nature of the epitope. Second, efficacy against the high pathology clinical isolate VR1814 was established on human foreskin fibroblasts (HFFs), human umbilical vein endothelia cell (HUVEC) and retinal pigmented epithelial cells (ARPE19) with a potency for all cell types of ~0.1 µg/mL. TRL345 activity on a broad range of cell types includes two key specialized placental cell types whose infection in vivo results in deficient growth of the placenta and thus of nutrient deprivation for the developing fetus: placental fibroblasts (maternal origin) and trophoblast progenitor cells (fetal origin). Third, HCMV can also spread by syncytial transfer. TRL345 did not fully prevent syncytial transfer but its efficacy was comparable to CMV-HIG but at ~10-fold lower concentration, and superior to a comprehensive set of other mAbs against various HCMV antigens. Fourth, because there is no adequate animal model for HCMV infection, the efficacy of TRL345 was evaluated using an *ex vivo* model; in this model, cytotrophoblasts grown on soft agar (Matrigel™) emigrate from cell columns to form anchoring villi that mimic the invasion of endometrium in vivo. VR1814 effectively infects these cells causing stunted growth of the invasive villi. To test the efficacy of antibody treatment, explants were infected at 12 hours after plating, treated with either TRL345 or CMV-HIG (human immune globulin) and fixed at 3 days post-infection. Neutralizing activity was measured in infected villous explants by counting the number of VR1814-infected cytotrophoblasts, which were visualized using a fluorescent tagged antibody to the viral immediate early (IE) antigen. TRL345 was ~50-fold more potent than CVM-HIG.

The gB AD-2 site is the most highly conserved region of the entire HCMV genome. The few variants in the TRL345 epitope discovered using next generation sequencing showed nearly all were conservative substitutions. Accordingly, escape from TRL345 is expected to be rare.

1.3 Nonclinical Pharmacology and Toxicology Studies

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

1.3.1 Pharmacology

Human cytomegalovirus (HCMV) is a member of the family Herpesviridae that also includes herpes simplex virus and Epstein-Barr virus. HCMV has co-evolved with humans over an extended timeframe [McGeoch 2000], and although 50-90% of adults are chronically infected with HCMV, it rarely causes harm because it is kept in check by the immune system. However, HCMV can become highly pathogenic in immunocompromised infants and may cause lethal infections,

especially in organ transplant or AIDS infants. Moreover, about 1% of susceptible women acquire a primary infection during pregnancy, with 40% of these women transmitting HCMV to their fetuses, contributing to stillbirth and to neurological defects, most commonly including deafness [Boppana 1995; Duff 2005].

HCMV replicates in vivo and in vitro in many different host cell types including epithelial cells, fibroblasts, connective tissue cells, hepatocytes, various leukocyte populations, and vascular endothelial cells. The broad host cell range makes it unclear if one protein or protein complex in the viral envelope is responsible in mediating entry into the host cell(s). More than 10 glycoproteins have been identified in HCMV particles as playing some role in the virus entry process including the essential glycoproteins gB, gH, gL, gM, and gN. These glycoproteins are being targeted for the development of vaccines or therapeutics (including monoclonal antibodies).

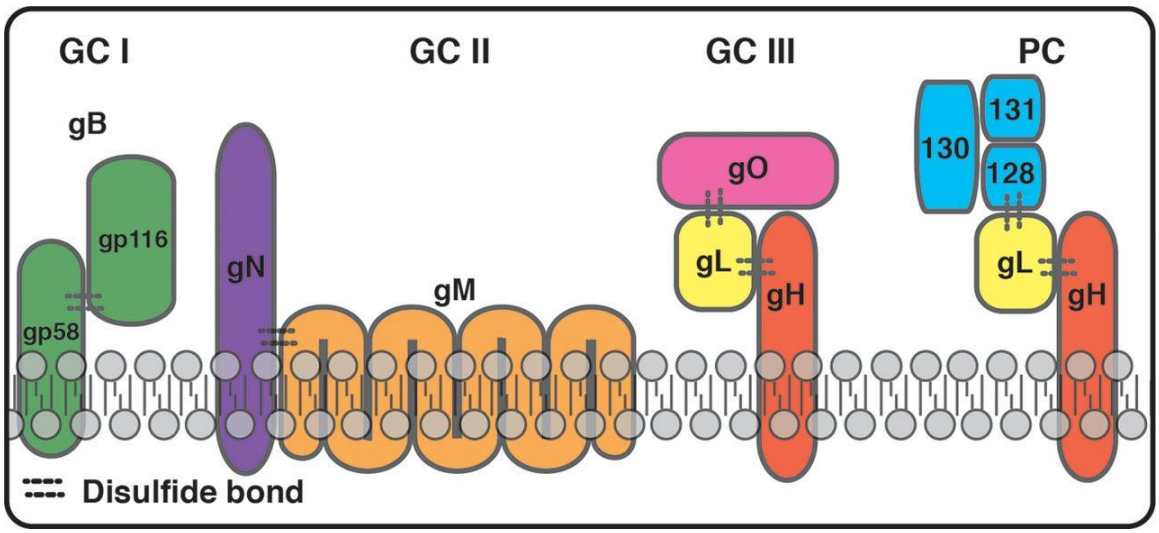

Figure 1: HCMV Glycoproteins as Vaccines or Therapeutic Targets
The essential CMV glycoprotein complexes required for cell attachment and entry are depicted. The glycoprotein complex (GC) designations are indicated. The pentameric complex (PC) is illustrated on the right and includes the UL128, UL130, and UL131a proteins. Parallel dashed lines represent disulfide linkages between individual envelope proteins. [Gardner 2016]

HCMV gB is a major envelope glycoprotein of HCMV encoded by the UL55 gene and has been clearly implicated in host cell entry, cell-to-cell virus transmission, and fusion of infected cells. In addition, it is an important target of both humoral and cellular immune responses [Pass 2009; Pötzsch 2011; Pang 2008].

Entry of HCMV into cells requires the conserved glycoprotein B (gB), thought to function as a fusogen and reported to bind signaling receptors. The crystal structure of the HCMV gB ectodomain has been determined to 3.6-Å resolution [Burke 2015]. The structure resembles the post-fusion structures of HSV-1 and EBV homologs. gB has a unique domain arrangement, demonstrating structural plasticity of gB that may accommodate virus-specific functional requirements.

- **Tissue Cross-Reactivity of TRL345 with Human Adult and Neonatal Tissues**

A GLP tissue cross-reactivity study of TRL345 using human adult and neonatal tissues was performed by Charles River Laboratories, (Reno, NV; Charles River Study # 20082357). The objective of this study was to determine the potential cross-reactivity of TRL345 with cryosections of human adult and neonatal tissues. This work was conducted by Charles River Laboratories under a service agreement with SRI International (Menlo Park, CA). A series of method development experiments was used to elucidate the optimal conditions for binding of TRL345 to control cell line sections. Following completion of the method development, the optimal binding of TRL345 was then applied at concentrations of 5.0 and 50.0 µg/mL. Panel of adult and fetal tissues evaluated are listed in **Table 1**.

Table 1: Panel of Tissues Evaluated for TRL345 Cross-Reactivity

Adult Human Tissues		
Adrenal	Lung	Spinal cord
Blood cells	Lymph node	Spleen
Blood vessels (endothelium)	Ovary	Striated (skeletal) muscle
Bone marrow	Fallopian tube (oviduct)	Testis
Brain, cerebrum (cortex)	Pancreas	Thymus
Brain, cerebellum	Parathyroid	Thyroid
Breast (mammary gland)	Peripheral nerve	Tonsil
Eye	Pituitary	Ureter
Gastrointestinal tract	Placenta	Urinary bladder
Heart	Prostate	Uterus- body (endometrium)
Kidney (glomerulus, tubule)	Salivary gland	Uterus, cervix
Liver	Skin	
Fetal Tissues		
Brain – Cerebral Cortex	Endothelium – Blood Vessels	Kidney
Liver	Lung	Ovary
Pancreas	Spleen	Thymus

Sporadic TRL345 binding was observed on epithelial cells in several adult (colon, skin, small intestine, and pancreas) and fetal (small intestine and pancreas) human tissues.

Consistent TRL345-specific staining (staining of 1 or more samples at 5 and 50 µg/mL) was observed in the cytoplasm, cell membrane and/or nuclei of colonic epithelium (3/3); small intestine epithelium (2/3); intercalated discs of heart myocytes (1/3 at 5 µg/mL; 3/3 at 50 µg/mL); adult liver bile duct epithelium (2/3); adult pancreas duct epithelium (2/3); epidermal keratinocytes, follicular and/or sebaceous gland epithelium, and/or superficial keratin in skin (3/3); cervix epithelium (1/3); bile duct epithelium of neonatal liver (1/3); and in duct epithelium and/or acinar cells of neonatal pancreas (2/2 at 50 µg/mL, 1/2 at 5 µg/mL).

Less consistent staining (1 or more samples at 50 µg/mL only) included cytoplasmic and/or nuclear staining in the granular cell layer of the cerebellum (3/3); corneal epithelium of the eye (2/3); epithelium, smooth muscle and/or fibromuscular cells of the Fallopian tube (3/3); epithelium, particularly gastric pits, smooth muscle cells of the muscularis externa, and submucosal vessels of the stomach (3/3); interstitial spindle cells and tubular epithelium in the kidney (1/3); placental villous mesoderm and endothelium (1/3); and connective tissue stromal cells in the prostate (1/3). Much of this inconsistent staining may be non-specific even though similar staining was not observed in matched negative controls. Staining in tissues with only 1 sample weakly positive at 50 µg/mL only (kidney, placenta, and prostate) is likely to be non-specific and not physiologically relevant.

Non-specific staining in several tissues confused interpretation of possible concurrent specific staining. These tissues included: liver (adult and neonatal), pancreas (adult and neonatal), salivary gland, pituitary, stomach, and skin.

Due to the widespread prevalence of chronic HCMV infection in humans, the observed sporadic binding is presumed to have been due to latent HCMV infections. That is, latent HCMV infection includes slow but persistent replication of the virus [Traylen 2011].

- **Homology of HCMV gB and TRL345 Binding Epitope within Human Proteome**

A BLAST search was performed to determine if any human proteins have significant homology to the HCMV gB protein (GenBank Protein Accession# CAA35414.1) or to the TRL345 binding epitope (ETIYNTTLKG). The BLAST search using TRL345 binding epitope resulted in over 900 hits. Within the hits, many had the same sequence pattern. All the sequences identified have amino acid substitutions or are missing amino acids that will significantly affect the binding of TRL345. Based on the BLAST search there are no human proteins that contain the TRL345 binding epitope.

To further evaluate potential of cross-reactivity as the source of the sporadic tissue reactivity staining, TRL345 was screened for binding against fixed and permeabilized human HEK293 cells, individually expressing 4417 human proteins comprising a comprehensive catalog of the human cell surface proteome (Retrogenix, Ltd). This screen revealed a set of 8 hits with potential recognition by TRL345, but no such binding could be confirmed. Moreover, the tissue distributions of these proteins did not match the TRL345 staining pattern.

- **Potential Off-Target Protein Binding by TRL345**

To evaluate potential of off-target protein binding as the source of the sporadic human tissue cross-reactivity staining, TRL345 was screened for binding against fixed and permeabilized human HEK293 cells, individually expressing 4417 human proteins comprising a comprehensive catalog of the human cell surface proteome (Retrogenix, Ltd). This screen revealed 8 hits by binding to solubilized cells with potential recognition by TRL345, but no such

binding could be confirmed by flow cytometry on live cells. Moreover, the tissue distributions of these proteins did not match the TRL345 staining pattern.

To further explore the possibility that TRL345 binds human proteins, an immuno-affinity extraction study was conducted. After extracting solubilized human proteins on a sorbent to which TRL345 was conjugated, the eluted proteins were analyzed by mass spectroscopy. Low homology to the TRL345 binding epitope among the eluted proteins was noted in 7 of the 54 unique skeletal muscle proteins (non-staining tissue by immunohistochemistry), 18 of the 197 unique pancreas proteins (positive staining) and 6 of the 414 proteins that were common to both the skeletal muscle and pancreas. The majority of the hit proteins are primarily intracellular. Homology to the TRL345 epitope was minimal for all of these, and none of them matched the tissue distribution of the staining observed in the TCR study.

Moreover, the toxicity study in rats did not reveal any toxicity signals for the gastrointestinal tissues in which binding in the human tissue cross reactivity study was observed. There were no signs of edema, no increase in inflammatory cells, and no abnormalities in clinical and hematology. The sparse binding of TRL345 in the pancreas tissue by immunohistology was only observed with the exocrine tissue (98% of the organ); no binding was observed to beta-cells (insulin producing cells).

The possibility of adverse off-target binding cannot be excluded. The main risk of adverse off-target binding is to the gastrointestinal tissues and pancreas, and includes the possibility of diarrhea, abdominal spasms and discomfort.

1.3.2 Pharmacokinetics

TRL345, administered as a single bolus IV injection at 10 mg/mL, was well tolerated in Sprague-Dawley rats. T_{max} occurred 5 minutes after the end of dosing and the C_{max} was 184 μg/mL. The elimination curve, accurately described by an open two compartment pharmacokinetic model, showed a short distribution phase with a $t_{1/2\alpha}$ of 3 hours and a longer elimination phase with a $t_{1/2\beta}$ of 46 hours. The volume of distribution (V_d) was approximately equivalent to plasma volume (60 mL/kg); however, the volume of distribution at steady state (V_{ss}), 305 mL/kg, indicated some distribution into the extravascular space. $AUC_{0\text{-}inf}$ was 1,642 μg*hr/mL. These data are consistent with other monoclonal antibodies and do not suggest that TRL345 accumulates in a specific tissue or that there is an "antibody sink."

1.3.3 Toxicology

The expected safety profile of TRL345 reflects three unusual factors. First, TRL345 is an IgG1 antibody that was cloned from human B cells. Comparable antibodies are present in CMV-HIG, which has been extensively tested in clinical trials [Kagan 2019]. Antibodies with the specificity

of TRL345 are present in CMV-HIG at a level of ~1-2%. In a variety of model systems, TRL345 was more effective than CMV-HIG at 50-fold lower dose.

Second, a human mAb with similar specificity as TRL345, but ~5-fold weaker affinity, successfully completed a Phase 1 clinical trial [TCN-202 from Theraclone, Inc; ClinicalTrials.gov Identifier: NCT01594437]. TCN-202 given at escalating doses from 1 mg/kg to 50 mg/kg was well tolerated throughout the study, with no dose-limiting toxicities or serious adverse events observed and demonstrated a favorable immunogenicity profile (no anti-TCN-202 antibodies were detected).

Third, antibodies against the same target protein are induced by the gB/MF59 vaccine which was well tolerated in clinical trials [Griffiths 2011]. In a Phase 2 placebo-controlled trial in solid organ transplant candidates, vaccination with gB plus MF59 adjuvant significantly boosted preexisting antibody levels against antigenic domain AD-2, which was correlated with decreased incidence of viremia [Baraniak 2018].

The safety of TRL345 was evaluated in a series of non-GLP and GLP in vivo studies. The administration of TRL345, to rats by twice weekly intravenous injection for 8 doses at dose levels of 0, 15, 50 or 150 mg/kg/dose was well-tolerated and did not result in any signs of overt toxicity. Clinical signs suggestive of a hypersensitivity-type reaction were observed after the 8th dose in the 15 and 50 mg/kg/dose animals. These clinical signs were considered secondary to the biological activity of the test item and were consequently not considered to be toxicologically significant. Over the 25-day treatment period, C_{max}, $AUC_{0\text{-}tlast}$ and AUC_{INF} values obtained on Day 25 from the Group 2 animals of both sexes were comparable to those obtained on Day 1, suggesting that TRL345 does not accumulate when administered twice weekly over a period of 4 weeks at doses $\leq$ 15 mg/kg/dose. However, C_{max}, $AUC_{0\text{-}tlast}$ and AUC_{INF} obtained on Day 25 from the Group 3 and 4 animals of both sexes were higher than those obtained on Day 1, as evidenced by the $AUC_{0\text{-}tlast}$ and AUC_{INF} accumulation ratios (2.1 to 5.9), suggesting that TRL345 has the potential to gradually accumulate when administered twice weekly over a period of 4 weeks at doses $\geq$ 50 mg/kg/dose.

There were no consistently marked sex-related differences in the measured TK parameters, except for T_{max} which appeared to occur later in males (1 hour post dose) as compared to females (5 minutes post dose). Anti-drug antibodies were detected in 13 out of 42 samples, but the presence of anti-human antibodies in the rat does not appear to have affected the test item's TK profile and is not considered relevant to administration of the human antibody to humans. Overall, there were no TRL345-related, toxicologically significant, effects on any of the other study parameters evaluated. The NOAEL for TRL345 was >150 mg/kg/dose; the safety margin is 15-fold compared to maximum starting human dose (MSHD) of 10 mg/kg and 5-fold compared to the maximum recommended high dose (MRHD) of 30 mg/mL proposed for the Phase 1 study [Clinical Protocol # TRL345-102].

No genotoxicity studies for TRL345 have been performed. Proteins are not typically considered to possess mutagenic potential based upon the inability to cross intact cell membranes, gain access to cytosolic/nuclear compartments, or integrate with or damage host cell DNA and alter host cell genetic material. Furthermore, there are no impurities contained in the final product formulation at levels high enough to be of mutagenic or carcinogenic concern.

No carcinogenicity studies for TRL345 have been performed. However, there was no evidence of abnormal cell proliferation or immunosuppression in cynomolgus monkeys after dosing with TRL345 IV twice weekly up to 150 mg/kg for 28-Days.

No developmental or reproductive toxicity studies with TRL345 have been performed. However, there was no evidence of macro- or microscopic changes in male or female organs from Sprague-Dawley rats dosed with TRL345 IV twice weekly up to 150 mg/kg for 28 days.

No effects attributable to formulated product were noted in Sprague-Dawley rats dosed with TRL345 IV twice weekly up to 150 mg/kg for 28-Days [ITR Study Report # 72460]. Given the excipients of the formulation buffer (i.e., 20 mM Histidine, 150 mM Sodium chloride, at pH 6.0) TRL345 is not expected to be irritating when administered IV.

1.4 Clinical Trials of Study Drug

No clinical trials of TRL345 have been conducted to date.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Assess the safety and tolerability of TRL345 when administered intravenously (IV) as a single dose in healthy adult volunteers

2.1.2 Secondary Objectives

The secondary objectives are to:

- Characterize the pharmacokinetics (PK) of a single IV infusion of TRL345 overall and by DG
- Assess the immunogenicity of TRL345 as measured by anti-drug antibodies (ADAs)

2.1.3 Exploratory Objective

The exploratory objectives are to:

- Explore the pharmacodynamics (PD) of TRL345 in an *ex vivo* study using serum samples to explore the capacity of various concentrations of TRL345 to neutralize HCMV in human serum
- Explore if there are any differences in adverse events, clinical labs, or PK across dose groups to explore if there are any signs of off-target binding of TRL345

2.2 Endpoints

2.2.1 Safety Endpoints

- Incidence and severity of abnormal physical exam findings, serum chemistries and hematology, vital signs (temperature, blood pressure, heart rate), adverse events, and incidence of serious adverse events

2.2.2 Pharmacokinetics

- C_{max}, C_{min}, CL, Vss, and T1/2 overall and by DG will be determined by ELISA

2.2.3 Immunogenicity

- Incidence of baseline and IP-emergent ADA (i.e., anti-TRL345 antibodies) in serum will determined by ELISA

2.2.4 Pharmacodynamics

- The proportion of samples with TRL345 concentrations within prespecified ranges that are associated with neutralization of HCMV in human serum

2.2.5 Exploration of Possible Off-Target Binding

- Gastrointestinal and CNS adverse events will be compared across DGs for any qualitative or quantitative differences in such events. LDH, hsCRP, IL-1alpha, estimated AUC, and estimated T1/2 will also be compared across DGs.

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 1, first-in-human, double-blind, single ascending dose study to assess the safety, PK, and PD of TRL345 in approximately 16 healthy male and female volunteers. Subjects aged 18-65, inclusive, will be screened.

Subjects will be assigned to a DG and randomized to receive TRL345 or placebo. There will be two dose groups. Each DG will be composed of 8 healthy volunteers; of these 6 will be randomized to receive TRL345 and 2 will be randomized to placebo. Any subject who withdraws before completing the study but after receiving IP may be replaced at the discretion of the Sponsor and in consultation with the Investigator. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

An established ELISA assay available in commercial laboratories to detect IgG antibodies against CMV will be used to determine serostatus of subjects.

Dosing of the first two subjects (one randomized to TRL345 and one randomized to placebo) in each DG will be done on the same day. Dosing of the other subjects will occur at least 72 hours after the first two subjects have been dosed and following review of the blinded safety data from the first two subjects in the DG by the PI and Sponsor. After all subjects within a DG have completed Day 15, a Safety Monitoring Committee (SMC) will review all available safety data through Day 15 prior to making a recommendation regarding escalation to the next higher DG.

Subjects will be admitted to a Phase 1 research unit prior to the IV administration of a single dose of IP. In order to maintain the blind, subjects will be dosed as follows: DG1 will receive 1 mg/kg of TRL345 or 0.1mL/kg of placebo and DG2 will receive 10 mg/kg of TRL345 or 1mL/kg of placebo. All subjects (randomized to either TRL345 or placebo) will receive IP infused over 60 minutes.

Subjects will be closely monitored for AEs and SAEs, including infusion reactions (IRs), from onset of the infusion through discharge from the Phase 1 research unit. Subjects will be assessed for safety and tolerability, including AEs and SAEs at each follow-up visit after discharge through Day 76. A physical exam, vital signs, and routine clinical lab tests (chemistry and hematology) will be done on Days 1, 2, 3, 8, 15, 29, and 43. An ECG will be done on Days 1 and 8.

Serum for PK will be collected on Days 1 (0, 1, 2, 4, 6, 12 hours after start of infusion), 2 (24 hours after start of infusion) and 3 (48 hours after start of infusion), and on Days 8, 15, 29, 43 and 76. Additionally, serum samples will be taken on Days 1, 8, 29, 43 and 76 for measurement of anti-TRL345 antibody levels. Samples taken on Days 1, 43, and 76 will be analyzed using an electrochemiluminescence assay. Samples collected on Days 8 and 29 will be held for exploratory analysis, if warranted, based on Day 43 and Day 76 ADA analysis results. The proportion of subjects with detectable anti-TRL345 antibody responses prior to dosing and IP-emergent anti-TRL345 antibodies will be reported.

Additional serum samples will be collected on Days 1 (pre-infusion and 1 hour after start of infusion), 15, 29, 43, and 76 for *ex vivo* PD assessments, which will be conducted at Professor McVoy's lab as defined in a separate protocol, whereby the dosed participants of the study will remain anonymous.

Additional serum samples will also be obtained on Days 1 (pre-infusion), 3, 8, 15, 29, and 43 for possible additional exploratory analyses that may be necessary to further explore any unexpected safety or tolerability observations.

3.2 Rationale for Study Design

3.2.1 General Design Issues

The study is double-blind and placebo-controlled to avoid bias and facilitate interpretation of findings in the TRL345 dose group as compared to the placebo group. Safety review by the SMC after all subjects within a DG have completed Day 15 minimizes risks to subjects to be subsequently dosed at the next higher dose.

3.2.2 Selection of Population

The selection of healthy volunteers ensures the ability to obtain safety, PK data, and provide samples for an *ex vivo* assessments of the relationship of PK to antiviral activity (PD data) of TRL345.

3.3 Selection of Dose

Doses for this study are as follows:

- Dose level 1: 1 mg/kg
- Dose level 2: 10 mg/kg

Selection of this dose range is based on the following considerations:

Since the molecular weight of TRL345 is greater than 100,000 Dalton's and the drug is administered intravenously, interspecies comparisons of doses can be made on a mg/kg basis, rather than on the basis of doses normalized for total body surface area (See the FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005).

The NOAEL was 150 mg/kg in a GLP repeat-dose toxicity study in Sprague-Dawley rats, which were dosed IV up to 150 mg/kg twice weekly for 28-days. The maximum recommended starting dose in humans of 10 mg/kg (Low Dose) has a safety margin of ~15-fold compared to the NOAEL in the rat.

Figure 1 depicts the modeled exposure curve in the Sprague-Dawley rat dosed at 150 mg/kg IV twice weekly for 28-days and shows the predicted TRL345 PK curves in humans after a single IV dose at 1.0 and 10.0 mg/kg.

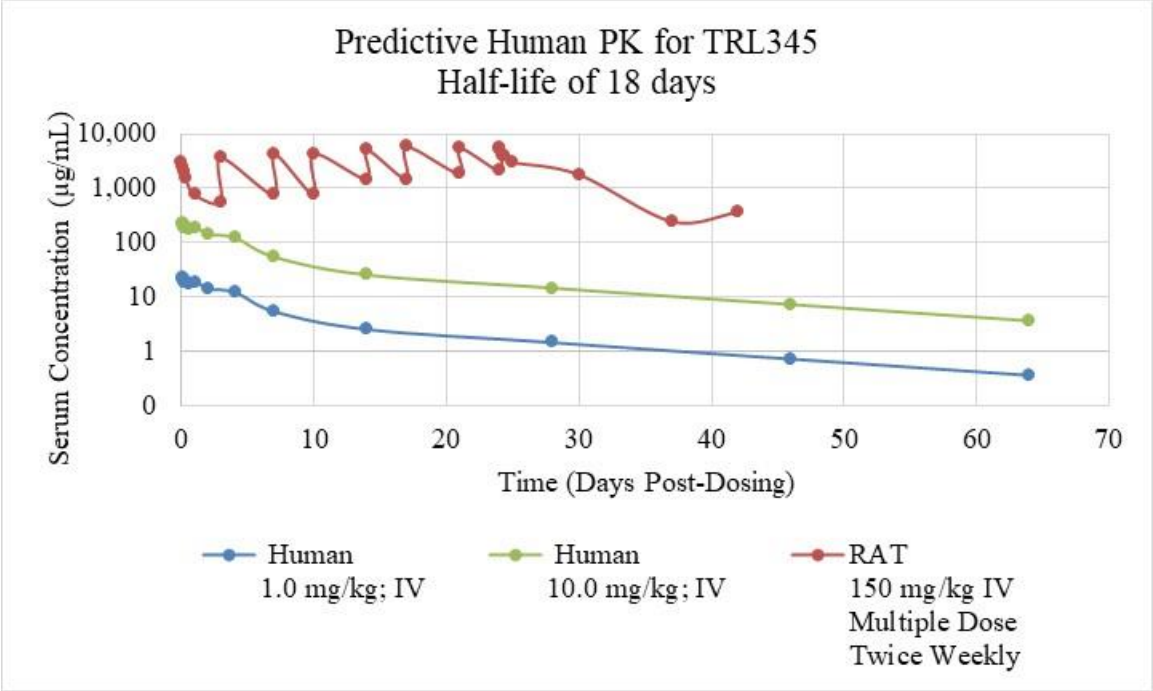

Figure 1: Comparative TRL345 Exposure in the Rat and Humans

3.4 Safety Monitoring

A Safety Monitoring Committee (SMC) will review safety, dose escalation and overall timelines.

They will review SAEs (Section 7.2.2) and ≥ Grade 3 AEs that are "Likely" (Section 7.2.3.) to be related to TRL345. Any infusion-related adverse events will be reported to the SMC within 24 hours. All data will be reviewed in an unblinded fashion upon completion of each DG.

The Sponsor will be responsible for notifying all study sites and Regulatory Authorities of any study recommendations, as appropriate.

3.5 Dose Escalation Criteria

The SMC will review all available safety data after the last subject in a DG has completed Day 15. They will evaluate the AEs, vital signs, and available laboratory results in the context of the established Study Pausing Rules (see below).

If Study Pausing Criteria are not met, they will make one of the following recommendations:

- Escalate to the next higher dose as planned
- Expand the DG to obtain additional safety information based on possible trends in laboratory assessments or Grade 1 (Mild) adverse events

3.6 Study Pausing Criteria

Should any one of the following criteria occur, the Sponsor will stop study recruitment and will not administer IP to any subject until the SMC has reviewed all available study data:

- First occurrence of an AE with severity Grade 3 (Severe) or Grade 4 (Potentially Life-Threatening) considered to be at least likely related to TRL345
- 2 or more subjects with an AE of severity Grade 2 (Moderate) in the same body class considered to be at least likely related to TRL345 (among total number of subjects dosed)
- Any other toxicity which in the opinion of the SMC precludes further dosing.

Following review of safety data, the SMC will make a recommendation to continue the study as planned, to modify, or to terminate the study.

3.7 Subject Participation and Study Duration

The total duration of enrollment is estimated to be 4 months. The duration of each subject's participation (including Screening) is approximately 12 weeks. Thus, the study is expected to last approximately 7 months.

4 SUBJECT POPULATION

Approximately 16 subjects who meet the eligibility criteria will be enrolled.

4.1 Inclusion Criteria

1. Healthy male and non-pregnant, non-breast-feeding female subjects at between 18 and 65 years of age, inclusive, and representative of the general population
2. Willing and able to provide written informed consent.
3. Availability for the entire duration of the study, and willingness to adhere to protocol requirements
4. In good health, as determined by lack of clinically significant abnormalities in health assessments performed at the Screening Visit, as judged by the Principal Investigator (PI) or as delegated by the PI to a physician or nurse practitioner as sub-investigator.
5. Men and women of child bearing potential (WOCBP) must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, or intrauterine device (IUD) for 28 days before Screening and through Day 76. Men must also refrain from donating sperm from Day 1 through Day 76.

4.2 Exclusion Criteria

1. Inability to tolerate blood draws or has poor venous access
2. Body mass index (BMI) <18.5 or ≥ 35 kg/m^2
3. Clinically significant vital sign abnormalities (systolic blood pressure lower than 90 or over 160 mmHg; diastolic blood pressure lower than 50 or over 100 mmHg; or, heart rate less than 45 or over 100 bpm) at the Screening Visit
4. ECG with clinically significant findings, including:
    a. Conduction disturbance (complete left or complete right bundle branch block or nonspecific intraventricular conduction disturbance with QRS $\geq$120 msec, PR interval $\geq$220 msec, any second- or third-degree atrioventricular block, or prolongation of the QT interval corrected according to Fridericia's correction [>450 msec male and >460 msec female])
    b. Significant repolarization (ST-segment or T-wave) abnormality; or
    c. Significant atrial or ventricular arrhythmia; or
    d. Frequent atrial or ventricular ectopy (e.g., frequent premature atrial contractions, 2 premature ventricular contractions in a row); or
    e. ST-elevation consistent with ischemia or evidence of past or evolving myocardial infarction.
5. Presence of any gastrointestinal pathology (e.g., chronic diarrhea, inflammatory bowel diseases), unresolved gastrointestinal symptoms (e.g., diarrhea, vomiting), or progressive liver or kidney disease

6. Diagnosis of diabetes mellitus
7. History of acute or chronic pancreatitis or upper right quadrant postprandial discomfort or pain within the last 2 years
8. Clinically relevant medical conditions that, in the opinion of the PI, may interfere with the evaluation of the trial drug, e.g., progressive cardiovascular disease
9. Concurrent acute or chronic infections (e.g., viral infections, except chronic recurrent herpes simplex infections)
10. Significant abnormal safety labs, defined as:
    - Greater than 30% outside of the normal range for any of the following: hemoglobin, white blood cell (WBC) count, platelet count, neutrophil count and blood urea nitrogen
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), direct bilirubin or indirect bilirubin >2 × the upper limit of normal
    - Activated partial thromboplastin time (aPTT) prolongation >1.5 x ULN
    - Hemoglobin A1C (HbA1C) >5.6%
    - Fasting glucose level of ≥100 mg/dl (5.6 mmol/L)
    - Renal function based on the, i.e., estimated creatinine clearance < 70 mL/min (Cockcroft-Gault formula using ideal body weight)
    - Hemoglobin ≤ 128 g/L (males) and ≤ 115 g/L (females), and hematocrit ≤ 37% (males) and ≤ 32.0% for females
11. Positive test results for HIV, Hepatitis B (HBsAg), or Hepatitis C (HCV) at the Screening Visit
12. History of significant drug abuse within one year prior to the Screening Visit and/or ongoing
13. History of significant alcohol abuse within one year prior to the Screening Visit defined as more than fourteen units of alcohol per week [one “unit” is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits)
14. Positive test for drugs of abuse, ETOH and nicotine (cotinine) at the Screening Visit
15. Positive serum beta-human chorionic gonadotropin test for pregnancy, pregnant, or nursing women
16. Unwilling to refrain from donating blood or plasma during the study.
17. Use of any new prescription medication or over-the-counter (OTC) product (including natural food supplements, vitamins, herbs) within 14 days prior to dosing
18. Receipt of any vaccine or booster within 14 days prior to Day 1 or planned vaccination or booster within 4 weeks after IP administration
19. Any planned medical intervention or personal event that might interfere with the ability to comply with the study requirements
20. Is current study site staff paid entirely or partially by the contract for this trial, or staff who are supervised by the PI or sub-PI

21. Receipt of an investigational product, or participation in another trial involving a marketed or investigational drug within 30 days of Day 1, or 5 half-lives of the investigational drug, whichever is longer
22. Any other comorbidity or condition that, in the opinion of the Investigator would make the subject unsuitable for the study or unable to comply with the study requirements

4.3 Subject and Study Discontinuation

4.3.1 Screening Failures

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

A subject who has failed screening may be rescreened at the discretion of the Investigator and Sponsor. In these cases, a new screening number must be assigned for each subject who is rescreened, and a new informed consent form must be signed.

4.3.2 Premature Discontinuation from Study

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

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

4.3.3 Replacement of Subjects

Any subject who withdraws before completing the study but after receiving IP may be replaced at the discretion of the Sponsor and in consultation with the Investigator. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

4.3.4 Study or Site Termination

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

- The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of Sponsor to suspend, discontinue, or shorten the study
- Study conduct at the study site may warrant termination under conditions that include the following:

- Failure of Investigator(s) to enroll eligible subjects into the study
- Failure of Investigator(s) to comply with International Conference of Harmonisation-Good Clinical Practice (ICH-GCP) guidelines, or FDA guidelines and regulations
- Submission of false information from the research facility to the Sponsor, the Clinical Monitor, the FDA, or Institutional Review Board (IRB)
- Insufficient adherence to protocol requirements
- A conflict of interest of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial
- Institution or IRB under investigation for cause by a regulatory agency

5 INVESTIGATIONAL PRODUCT

5.1 TRL345

TRL345 is a human IgG1kappa (G1m1,17 (z,a); Km3 allotype) monoclonal antibody cloned from human B lymphocytes which targets the highly conserved AD-2, Site I epitope on the gB viral glycoprotein of the Human Cytomegalovirus (HCMV).

TRL345 is not intended to be administered as a therapeutic, i.e., antiviral agent.

5.1.1 Packaging and Labeling

TRL345 is manufactured, packaged, and labeled by the Sponsor's designee(s) in accordance with legal and regulatory requirements.

TRL345 is formulated as a sterile, clear, preservative-free solution and is packaged in a single-use vial for IV administration. Each vial contains 10 mL of TRL345 at 10 mg/mL.

TRL345 will be distributed to each site by the Sponsor or its designee.

The label is as follows:

5.1.2 Storage

TRL345 will be stored at 2ºC to 8ºC (36ºF to 46ºF).

5.2 Placebo

The placebo for this study is available 0.9% Sodium Chloride Injection USP (normal saline).

5.2.1 Packaging and Labeling

Commercially available 0.9% Sodium Chloride Injection USP (normal saline) in IV bags will be used. These will be provided by the Sponsor if not available at a participating study site.

5.2.2 Storage

Placebo should be stored at in accordance with the product label.

5.3 Preparation of Investigational Product

Preparation of the TRL345 and placebo must be performed by a designated **unblinded** site pharmacist (or otherwise qualified personnel) in accordance with the Pharmacy Manual provided by the Sponsor.

The dose of TRL345 will be determined by subject weight at the Day 1 visit. In order to maintain the blind, subjects will be dosed as follows: DG1 will receive 1 mg/kg of TRL345 or 0.1mL/kg of placebo and DG2 will receive 10 mg/kg of TRL345 or 1mL/kg of placebo. All subjects (randomized to either TRL345 or placebo) will receive IP infused over 60 minutes.

5.4 Administration of Investigational Product

IV administration of TRL345/placebo will be performed by **blinded**, trained, and qualified site personnel. A calibrated IV infusion pump will be set to deliver the total volume of IP over a 60-minute period. Start and stop times will be recorded in the subject record and eCRF.

5.5 Blinding and Unblinding

Investigators, subjects, and all study staff with direct subject contact will be blinded to treatment assignment. A designated **unblinded pharmacist** (or otherwise qualified personnel) at each site will prepare each dose. That individual should have no contact with the subjects and minimize contact with other site study personnel.

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

5.6 Investigational Product Accountability

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

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

5.7 Management of Infusion Reactions

It is required that all sites have the personnel, equipment, and medications to manage hypersensitivity reactions. Subjects must be monitored closely for signs and symptoms of an infusion reaction (IR) (e.g., fever >38°C (100.4°F), chills, flushing, bradycardia, hyper- or hypotension, itching, flushing urticaria, nausea, vomiting, abdominal pain, chest tightness, angioedema, or respiratory distress). In the event of an IR, the infusion should be slowed or stopped and restarted at the discretion of the Investigator. If a severe IR occurs (Grade 3 or 4 signs or symptoms), discontinue infusion and institute treatment as appropriate. Any infusion-related adverse event will be reported to the SMC within 24 hours.

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

- A targeted physical examination to capture medically relevant details, including but not limited to, a thorough dermatologic examination; a chest examination for breath sounds, stridor or wheezing; and a cardiac examination with attention to irregular heartbeat.
- Vital signs (sitting or supine blood pressure, heart rate, and body temperature) will be captured at the time of the IR and at least every 15 minutes until the resolution or stabilization of the IR. In addition, hematology and serum chemistry will be taken.

The Investigator may administer any medically indicated pharmacologic agent or procedure intended to relieve symptoms. Signs and symptoms of the IR and drugs given for treatment are to be recorded in the medical record and in the separate electronic case report form (eCRF) page for possible and probable IRs.

5.8 Prior and Concomitant Medications

Subjects may not receive any vaccine or booster within 14 days prior to Day 1 or planned vaccination or booster within 4 weeks after IP administration.

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

5.9 Other Study Restrictions

5.9.1 Birth Control

Men and WOCBP must be willing to practice a highly effective method of contraception that may include, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with vasectomized partner, vasectomy, hysterectomy, bilateral tubal ligation, licensed hormonal methods, or IUD for 28 days before Screening and through Day 76. Men must also refrain from donating sperm from Day 1 through Day 76.

5.10 Treatment Compliance

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

6 STUDY PROCEDURES

Refer to Schedule of Events Table.

6.1 Definitions and Descriptions of Assessments and Procedures

Medical history – medical history will be obtained by way of subject interview and medical records. All clinically significant past and current medical history will be obtained. Clinically significant history includes those illnesses/diagnoses that are/were treated with medication for more than 14 days or other medical intervention (e.g., hospitalization, surgery, physical therapy, etc.).

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

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

12-lead ECG – after a subject has been supine for 5 minutes, triplicate ECGs will be obtained over 5 minutes. 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). QTcF will also be determined. Subjects may not use tobacco or nicotine within 4 hours prior to the ECG.

Vital Signs – temperature, heart rate, blood pressure. Heart rate and blood pressure should be obtained after subject is resting for 5 minutes. Height will be obtained at Screening only. Weight will be obtained at Screening, on Day 1, and at Day 43.

Serum chemistry – sodium, potassium, chloride, carbon dioxide (CO2), urea nitrogen (BUN), creatinine (CREA), calcium, glucose, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT). HsCRP and LDH will be assessed at Days 1, 15, and 29 only.

Hematology – hemoglobin, red blood cell count, white blood cell count with differential, platelet count.

Hemoglobin A1c – whole blood sample at Screening

Additional safety assessments – amylase, lipase, creatine kinase, NT-proBNP, IL-1α, fasting glucose, fasting blood insulin. Subjects must refrain from strenuous exercise within 5 days prior to assessment of creatine kinase.

CMV serology – an established ELISA assay available in commercial laboratories to detect IgG antibodies against CMV will be used to determine serostatus of subjects.

Urine drug test – amphetamines (includes methamphetamines and ecstasy/methylenedioxymethamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine

metabolites, cotinine, ethyl alcohol, methadone, methamphetamines, opiates (including heroin, codeine, and oxycodone/oxymorphone)

Women of childbearing potential (WOCBP) – not surgically sterile or post-menopausal defined as age > 40 years without menses for ≥ 2 years without an alternative medical cause for amenorrhea.

AEs, SAEs – refer to Section 7.2.

Infusion reaction (IR) – refer to Section 5.7.

6.2 Screening

At the time of screening, each subject will be assigned a sequential subject identification number (Subject ID).

The following assessments and procedures will be performed:

Written informed consent

Verification of eligibility

Demographics

Medical/Disease history, including review of concomitant medications

Complete physical exam, including, an assessment of venous access

Vital signs including height, and weight

12-lead ECGs in triplicate (subjects may not use tobacco or nicotine within 4 hours prior to the ECG)

Laboratory Evaluations, including:

- Serum chemistry
- Hematology
- Fasting glucose
- HbA1c
- CMV serology
- Serum pregnancy test in WOCBP
- Serology for HIV, hepatitis B and C
- Urine drug test

Schedule Day 1 visit

6.3 Randomization

Subjects who meet all inclusion and no exclusion criteria, will be sequentially enrolled into the study, assigned to DG, and randomized to receive TRL345 or placebo. Each DG will include 8 subjects (6 will be randomized to TRL345 and 2 to placebo).

Randomization code numbers will be allocated to subjects after assessment of eligibility. The randomization list will be generated by a standard software program and the randomization process will be conducted in accordance with the Standard Operating Procedures (SOPs) of the Clinical Research Organization (CRO).

6.4 On-Study Procedures

6.4.1 Study Day 1

The following procedures will be performed prior to administration of IP:

Reconfirm eligibility

Targeted physical exam

Concomitant medication assessment

Laboratory Evaluations, including:

- Serum chemistry (including hsCRP and LDH)
- Hematology
- Amylase, lipase, and creatine kinase (subjects must refrain from strenuous exercise within 5 days prior to assessment of creatine kinase)
- Fasting glucose
- Fasting blood insulin level
- NT-proBNP and IL-1α
- Serum for PK, PD, ADA, and possible exploratory analyses (see additional times below for PK and PD)

The following procedures will be performed at the times specified below:

Vital signs within 60 minutes prior to dosing and then at 15, 30, and 60 minutes (end of the infusion), and 1 and 4 hours after the end of the infusion

Serum for PK will be obtained at prior to the start of infusion and then at end of infusion (60 minutes), and 2, 4, 6, 12, 24 (Day 2), and 48 hours (Day 3) after the start of the infusion

Serum for PD will be obtained at prior to start of infusion and then at end of infusion (60 minutes)

12-lead ECGs in triplicate within 4 hours post-completion of infusion (subjects may not use tobacco or nicotine within 4 hours prior to the ECG)

Additionally, the following will be performed:

Randomization of the subject to study/DG

Intravenous dosing of study IP per randomization assignment. A calibrated IV infusion pump will be set to deliver the total volume of IP over a 60-minute period.

Adverse events will be assessed during and after the infusion.

6.4.2 Study Days 2 and 3

The following procedures will be performed:

Targeted physical exam

Vital signs

Laboratory Evaluations, including:

- Serum chemistry
- Hematology
- Amylase, lipase, and creatine kinase (subjects must refrain from strenuous exercise within 5 days prior to assessment of creatine kinase) (Day 3 only)

- Fasting glucose (Day 3 only)
- Fasting blood insulin level (Day 3 only)
- Additional serum sample for possible exploratory analyses (Day 3 only)
- NT-proBNP and IL-1α (Day 3 only)
- Serum for PK

AE assessment

Concomitant medication assessment

6.4.3 Study Day 8 (± 1 day)

The following procedures will be performed:

Targeted physical exam

Vital signs

Laboratory Evaluations:

- Serum chemistry
- Hematology
- Amylase, lipase, and creatine kinase (subjects must refrain from strenuous exercise within 5 days prior to assessment of creatine kinase)
- Fasting glucose
- Fasting blood insulin level
- Serum for PK, ADA, and possible exploratory analyses (ADA to be held for exploratory analysis, if warranted)

12-lead ECGs in triplicate (subjects may not use tobacco or nicotine within 4 hours prior to the ECG)

AE assessment

Concomitant medication assessment

6.4.4 Study Days 15 (± 2 days) and 29 (± 3 days)

The following procedures will be performed:

Targeted physical exam

Vital signs

Laboratory Evaluations:

- Serum chemistry (including hsCRP and LDH)
- Hematology
- Amylase, lipase, and creatine kinase (subjects must refrain from strenuous exercise within 5 days prior to assessment of creatine kinase) (Day 15 only)
- Fasting glucose
- Fasting blood insulin level
- NT-proBNP and IL-1α

- Serum for PK, PD, ADA, and possible exploratory analyses (ADA at Day 29 to be held for exploratory analysis, if warranted)

AE assessment

Concomitant medication assessment

6.4.5 Study Day 43 (± 3 days) or Early Termination

The following procedures will be performed:

Targeted physical exam

Vital signs including weight

Laboratory Evaluations:

- Serum chemistry
- Hematology
- Fasting glucose
- Fasting blood insulin level
- NT-proBNP and IL-1α
- Serum for PK, PD, ADA, and possible exploratory analyses
- Serum pregnancy test in WOCBP

AE assessment

Concomitant medication assessment

Overall status

6.4.6 Study Day 76 (± 5 days)

The following procedures will be performed:

Laboratory Evaluations:

- Serum for PK, PD, and ADA

AE assessment

Concomitant medication assessment

Overall status

6.5 Research Specimens

Additional serum samples are taken for *ex vivo* PD assessments. These assessments will be conducted as defined in a separate protocol, whereby the dosed participants of the study will remain anonymous.

Blood for future research will be obtained on those days PK samples are taken. These PK samples and the additional serum samples for any exploratory assessments are mandatory as part of participation in this study. The PK samples, if not required for repeat of PK assessments, may be retained for future exploratory assessments. These stored samples will remain anonymized

and may be used by the Sponsor or its research partners for retesting of planned tests, characterization of TRL345, further analyses to study CMV infections, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed on these samples. At the conclusion of this study, these samples may be retained in storage by the investigators, Sponsor or its research partners for a period up to 15 years.

7 ADVERSE EVENTS

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

7.1 Reporting Responsibilities

All AEs, including SAEs, will be recorded in the eCRF from start of IP infusion through Study Day 76. It is the responsibility of the Investigator or Sub Investigator(s) to perform assessment of AEs and SAEs at each study visit. Data describing AEs, and SAEs, will be entered in the subject's medical record and eCRF. SAEs will be reported to the Sponsor as described in Section 7.6.

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

7.2 Definitions

7.2.1 Adverse Event

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

7.2.2 Serious Adverse Event

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

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

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
    - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room (ER) or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

7.2.3 Relatedness (Causality)

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

Likely - Reasons to consider an AE likely related to treatment may include, but are not limited to the following:

- Timing of the event relative to the administration of the IP
- Location of the AE relative to the site of IP administration
- Likelihood based on experience with similar products
- There is a biologically plausible explanation based on the mechanism of action or mode of delivery of the treatment
- The AE is repeated on subsequent treatments
- No other explanation is likely

Unlikely - An AE with no temporal association with the IP but rather related to other etiologies such as concomitant medications or conditions, or subject's known clinical state.

7.2.4 Severity

Each sign or symptom reported will be graded according to the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (https://www.fda.gov/media/73679/download).

7.3 Clinical Laboratory Abnormalities

Any laboratory abnormality deemed clinically significant by the Investigator should be reported as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Screening/Baseline so that in the judgment of the Investigator a change in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the medical diagnosis rather than a laboratory value (e.g., “anemia” rather than “low Hb”) should be reported as the AE term. Repeated additional tests and/or other

evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

7.4 Physical Exam Abnormalities

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

7.5 Pregnancy

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

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

7.6 Reporting of Serious Adverse Events

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

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

7.7 Follow-Up of Adverse Events

Any subject experiencing an AE, including clinically significant abnormal laboratory result or physical exam finding, will be monitored at appropriate intervals (e.g., weekly for laboratory abnormalities) until resolution or stabilization, or until a time that is mutually agreed upon between the Medical Monitor and the Investigator.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size

No formal sample size calculations were performed. The numbers of subjects per dose level are typical for Phase 1 studies in healthy adult volunteers.

8.2 Analysis Conventions

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

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

No imputation of values for missing data will be performed.

All safety, pharmacokinetic, and immunogenicity data will be included in data listings and summaries.

8.3 Analysis Populations

All subjects receiving IP will be included in all analyses.

8.4 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose and treatment group and consist of (but not limited to) the following: age, height, weight, sex, ethnicity/race, and disease history. Additionally, the number and percent of subjects with past and current medical disorders (i.e., Medical History) at Screening will be presented overall and by dose group.

8.5 Safety Analyses

8.5.1 Adverse Events

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

AEs and SAEs will be summarized overall, by severity, and relatedness, and may also be summarized within specific time intervals (e.g., within 4 hours of infusion).

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

8.5.2 Laboratory Evaluations and Vital Signs

Quantitative data (e.g., clinical lab results) will be summarized by presenting mean, median, SD, and range by dose and treatment group. Laboratory abnormalities will be analyzed as safety outcomes by summarizing frequency, severity, and changes from baseline. Other analyses may include but are not limited to the following: examination of shift tables and pre-established severity grades. Additional serum samples will be taken and stored for possible exploratory analyses that may be necessary to further explore any unexpected safety or tolerability observations.

8.5.3 Concomitant Medications

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

8.6 Pharmacokinetic and Immunogenicity Analyses

Individual subject TRL345 serum concentrations and derived PK parameters will be summarized using descriptive statistics.

Pharmacokinetic parameters to be evaluated during this study include C_{max}, C_{min}, CL, Vss, T½,

Anti-TRL345 antibodies will be summarized with descriptive statistics by dose group.

8.7 Pharmacodynamic Analysis

Ex vivo PD analysis will be done at Professor Michael McVoy's lab (Professor of Pediatrics, Virginia Commonwealth University, Richmond, VA 23298 USA) as defined in a separate protocol.

9 ETHICAL AND ADMINISTRATIVE RESPONSIBILITIES

9.1 Ethical Conduct of the Study

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

9.2 Institutional Review Board Approval

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

9.3 Informed Consent

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

9.4 Confidentiality

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

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

9.5 Protocol Amendments

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

9.6 Case Report Forms

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

9.7 Source Document Maintenance

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

9.8 Retention of Records

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

9.9 Study Monitoring

Site visits will be conducted by an authorized Sponsor representative (the monitor) to inspect study data, subjects' medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the respective US or national regulations and guidelines, as applicable. It will be the monitor's responsibility to inspect the eCRFs, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRFs. Visits will occur at the initiation of the study, following enrollment of the first subject, and approximately 4 to 6 weeks thereafter.

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

9.10 Protocol Deviations

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

- Subject did not meet study eligibility criteria
- Subject did not receive treatment assignment per randomization scheme
- Subject received the wrong dose TRL345 (> ±20% of assigned dose)
- Subject received a prohibited concomitant medication (i.e., any vaccine within 14 days prior to Day 1 or planned vaccination within 4 weeks after IP administration)

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

9.11 Financial Disclosure

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

9.12 Publication and Disclosure Policy

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

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

The Sponsor adheres to the general principles of publication of scientific data as articulated by the International Committee of Medical Journal Editors and acknowledges its responsibility to

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

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

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AMENDMENT TO THE PROTOCOL

Amendment X, Protocol Version X.0, DAY MONTH 20YY

The overall purpose of the amendment is to:

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Summary of Changes

Section	**Change**	**Rationale**