CLINICAL STUDY PROTOCOL

This study will be conducted according to this protocol, including protocol amendments and in compliance with Good Clinical Practice, the ethical principles, and other applicable regulatory requirements

Protocol Number:	**TRS00301001**
Clinical Phase:	**Phase 1**
IND Number:	**136545**
Sponsor:	**Zhejiang Teruisi Pharmaceutical Inc.**
Version:	**1.0**
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SPONSOR SIGNATURE

Study Title: A randomized, double-blind, single-dose, three-arm, parallel-group, phase 1 study to compare pharmacokinetic and safety of TRS003 to China-approved bevacizumab and US-licensed Avastin, when administered intravenously to healthy male subjects.

Protocol Number: TRS00301001

Version: 1.0

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Zhejiang Teruisi Pharmaceutical Inc.

_____

Signature by: Youling Wu, Ph.D.

_____

Date

INVESTIGATOR AGREEMENT

I have read Protocol TRS00301001: "A randomized, double-blind, single-dose, three-arm, parallel-group, phase 1 study to compare pharmacokinetic and safety of TRS003 to China-approved bevacizumab and US-licensed Avastin, when administered intravenously to healthy male subjects" and agree to conduct the study as described therein in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

The signature below constitutes my agreement to the contents of this protocol.

_____

Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AHA	Autoimmune Hemolytic Anemia
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Transaminase
AUC	Area under the serum concentration-time curve
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EOI	End-of-Infusion
EOS	End-of-Study Visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C virus

HBsAg	Hepatitis B Surface antigen
HbcAb	Hepatitis B core antibody
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion Related Reaction
IV	Intravenously
MedDRA	Medical Dictionary for Regulatory Activities
PE	Physical Examination
PK	Pharmacokinetics
SAE	Serious Adverse Event
SD	Standard Deviation
ULN	Upper Limit of Normal
UP/CR	Urine Protein to Creatinine Ratio
WBC	White Blood Cells

SYNOPSIS

Title	A randomized, double-blind, single-dose, three-arm, parallel-group, phase 1 study to compare pharmacokinetic and safety of TRS003 to China-approved bevacizumab and US-licensed Avastin, when administered intravenously to healthy male subjects.
Sponsor	Zhejiang Teruisi Pharmaceutical Inc.
Study Drug	TRS003
Clinical Trial Phase	Phase 1
Proposed Indication	Metastatic colorectal cancer (mCRC); First-line Non-Squamous Non-small cell lung cancer (NSCLC); Recurrent Glioblastoma (GB) in adults; Metastatic renal cell carcinoma (mRCC); Persistent, Recurrent or Metastatic carcinoma of the cervix ; recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.
Objectives	Primary • To demonstrate pharmacokinetic (PK) similarity between TRS003, China-approved bevacizumab and US-licensed Avastin, as measured by $AUC_{0\text{-}inf}$ in healthy male subjects after a single 3 mg/kg dose. Secondary • To assess other PK parameters such as but not limited to C_{max} and AUC_{last}, following a single dose of TRS003, China-approved bevacizumab and US-licensed Avastin in healthy male subjects. • To determine the incidence of immunogenicity against TRS003, China-approved bevacizumab, and US-licensed Avastin in healthy male subjects. • To evaluate the safety of TRS003, China-approved bevacizumab and US-licensed Avastin in healthy male subjects.
Study Population	18-55 yrs. healthy male volunteers
Sample Size	Assuming a CV of 20% (Knight et al., 2016) in male healthy subjects and 1.05 for the geometric mean ratio (TRS003/ China-approved bevacizumab/US-licensed Avastin®/) of $AUC_{0\text{-}inf}$, the study with 29 evaluable subjects per arm will have 95% power to demonstrate the PK similarity between TRS003, China-approved bevacizumab, and US-licensed Avastin (90% confidence interval [CI] of geometric mean ratio within 80-125%). Assuming a 15% drop out rate (including non-evaluable subjects) and a 95% power, approximately

	114 subjects (38 per arm) will be randomized in 1:1:1 ratio to ensure adequate power to demonstrate PK similarity using 3 pairwise comparisons.
Number of Study Centers Planned	Approximately 1-3 study sites located in the United States. Additional sites may be added if necessary.
Study Design	This is a 12-week, randomized, double-blind, single-dose PK study. Approximately 114 healthy male subjects (screening occurred within 28 days prior to dosing) will be randomized 1:1:1 to either TRS003, China-approved bevacizumab, and US-licensed Avastin groups. Study drug will be dispensed as a single 3 mg/kg dose for intravenous infusion within 90 minutes. PK and immunogenicity samples will be collected and safety will be assessed.
Pharmacokinetic (PK) and Immunogenicity evaluations	For details for PK and immunogenicity sample collections refer to Schedule of Activities. If a sample is positive in the screening assay, a confirmatory assay will be conducted. If a confirmatory assay is positive, the titer and the neutralization activity will be tested. Teruisi is conducting the assay validation for PK and anti-drug antibody (ADA) assays according to FDA Guidance, "Bioanalytical Method Validation May 2013".
Safety Evaluations	Safety will be assessed by periodic physical examination findings, vital signs, clinical laboratory tests, 12-lead ECGs, and AEs.
Statistical Analysis	Safety population consists of all subjects who received the investigational product. PK population consists of all subjects who have evaluable concentration-time data. Descriptive statistics of PK parameters (geometric mean, CV%, arithmetic mean, median, SD, minimum and maximum) will be provided. The primary assessment of PK similarity will be based upon a 90% CI for the ratio of the geometric means (TRS003, China-approved bevacizumab and US-licensed Avastin) for $AUC_{0\text{-}inf}$ on PK analysis set. If the 90% CI of the ratio of the geometric means for $AUC_{0\text{-}inf}$ is within the range of 80-125%, then PK similarity will be concluded. Secondary PK parameters such as but not limited to C_{max}, AUC_{last} will be analyzed using the same statistical approach. A nonparametric approach, for example, Wilcoxon signed-rank test, will be taken to evaluate parameters such as $t_{1/2}$. Exploratory analyses may be performed for other PK parameters as deemed appropriate.

All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and association with the study drugs. Clinical laboratory parameters, vital signs, and ECG parameters will be listed and summarized using descriptive statistics. The number and percentage of subjects testing positive for ADAs will be summarized by treatment and time point.

Table 1 Schedule of Activities

Protocol Activity			Clinical Research Unit (CRU) Confinement							Outpatient Visits								
	Screen -D28 to – D2	-D1	Pre-dose D1	0h Infusion	0h Post EOI	0.5 hour* Post EOI	4h ±10 min	8h ±10 min	24h D2 ±1h	48h D3 ±4h	96h D5 ±8h	168h D8 ±8 h	336h D15 ±1 day	672h D29 ±2 days	1008h D43 ±2 days	1344h D57 ±2 days	1680h D71 ±2 days	2016h D85 (EOS) ±2 days
Signed Informed Consent (ICF)[1]	×																	
Inclusion/Exclusion Criteria	×	×																
Demographics[2]	×																	
Weight[3]	×	×																×
Medical History	×																	×
Physical Examination	×	×							×					×		×		×
Current Medications/OTC/supplements	×	×												×		×		×
Vital Signs[4]	×	×		×	x	×	x	x	×	×		×		×		×		×
12 Lead Electrocardiogram (ECG)[5]	×					×												×
Alcohol breath test	x	x																
Adverse Events (AE)	×	Ongoing																
Laboratory Tests																		
Hematology & Serum Chemistry[6]	×	×							×			×		×		×		×
Coagulation Tests[7]	×																	
Screening for HIV, HBV, HCV[8]	×																	

Protocol Activity			Clinical Research Unit (CRU) Confinement							Outpatient Visits								
	Screen -D28 to – D2	**- D1**	**Pre-dose**	**0h Infusion**	**0h Post EOI**	**0.5 hour Post EOI**	**4h ±10 min**	**8h ±10 min**	**24h D2 ±1h**	**48h D3 ±4h**	**96h D5 ±8h**	**168h D8 ±8 h**	**336h D15 ±1 day**	**672h D29 ±2 days**	**1008h D43 ±2 days**	**1344h D57 ±2 days**	**1680h D71 ±2 days**	**2016h D85 (EOS) ±2 days**
Urinalysis (U/A)[9]	×								×			×		×		×		×
Urine drug screen	**X**	**X**																
Administration of TRS003//China approved bevacizumab or US -Licensed Avastin				×														
Pharmacokinetics (PK)[10]			×		**X**	×	×	×	×	×	×	×	×	×	×	×	×	×
Anti-Drug Antibodies (ADA) [11]			×										×	×		×		×

EOS=End of Study; EOI=End of Infusion; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; D=Day

*0.5 h post EOI is 2 h post the start of infusion if the infusion starts at 0 and ends at 90 min

1. Written consent must be obtained prior to performing any protocol specific procedure.
2. Age, height, gender, ethnicity, and race at screening where possible
3. Body weight will be measured at screening and -D1 and D85.
4. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Vital signs will be assessed at supine position at screening and on the visits at the clinical research unit. Vital sign will be performed within 30 minutes prior to the infusion. Additionally, vital signs will be taken before every PK sampling.
5. ECGs (single ECG only) will be collected at screening, within 30 minutes post EOI, and as clinically indicated, and at EOS. The subjects should take supine position.
6. Hematology includes Complete blood count (CBC) (hematocrit (HCT), hemoglobin, red blood cells (RBC), Red Cell Distribution Width (RDW), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), platelets, white blood cells (WBC) with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). Serum Chemistry ALT, AST, ALP, K+, Na+, Cl-, Ca2+, TBIL, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted), albumin. Assessments will be performed on screen, within 72 hours prior to dosing (if the labs are ⩾3weeks old), and on D2, D8, D29, D57 and D85.
7. INR/PT and aPTT: Assessments will be performed on screening.
8. HIV screening (Antigen/antibody test), HCV antibodies, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), total hepatitis B core antibody (anti-HBc), IgM antibody to hepatitis B core antigen (IgM anti-HBc).
9. Dipstick is acceptable. Assessments will be performed on screening and on D2, D8, D29, D57 and D85.
10. PK samples will be collected at pre-dose, 0 h (at EOI), 0.5h, 4h, 8h, 24h (Day 2), 48h (Day 3), 96h (Day 5), 168h (Day 8), 336h (Day 15), 672h (Day 29), 1008h (Day 43), 1344h (Day 57), 1680h (Day 71), and 2016h (Day 85) hours post EOI

11. Blood samples for ADA analyses will be collected at pre-dose, 336h (Day15), 672h (Day 29), 1344h (Day 57) and 2016h (Day 85) hours after EOI.

Table 2 Approximate Blood Volumes (mL) Sampled During the Study

Protocol Activity			Clinical Research Unit (CRU) Confinement							Outpatient Visits								
	Screen -D28 to – D2	- D1	Pre-dose	0h Infusion	0h Post EOI	0.5 hour* Post EOI	4h ±10 min	8h ±10 min	24h D2 ±1h	48h D3 ±4h	96h D5 ±8h	168h D8 ±8 h	336h D15 ±1 day	672h D29 ±2 days	1008h D43 ±2 days	1344h D57 ±2 days	1680h D71 ±2 days	2016h D85 (EOS) ±2 days
Initial Screening Labs (mL)	12																	
Hematology & Serum Chemistry (safety labs) (mL)		10[1]							10			10		10		10		10
Pharmacokinetics (PK) (mL)			6		6	6	6	6	6	6	6	6	6	6	6	6	6	6
Anti-Drug Antibodies (ADA) (mL)			8										8	8		8		8
Total Amount per visit (mL)	12	10	14		6	6	6	6	16	6	6	16	14	24	6	24	6	24

1. Hematology includes Complete blood count (CBC) (hematocrit (HCT), hemoglobin, red blood cells (RBC), Red Cell Distribution Width (RDW), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), platelets, white blood cells (WBC) with absolute differential counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils). Serum Chemistry ALT, AST, ALP, K+, Na+, Cl-, Ca2+, TBIL, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted), albumin. Assessments will be performed within 72 hours prior to dosing (if the labs are ⩾3weeks old).

1 INTRODUCTION

1.1 BACKGROUND

Angiogenesis is a rate-limiting step in multiple pathological processes and is also one of the hallmarks of cancer growth and development. Therefore, angiogenesis has emerged as a valid therapeutic target in the field of oncology. As the tumor grows, tumor initiates the process called "angiogenic switch", that shifts the balance between angiogenesis inhibitors and stimulators, by stimulating the production of angiogenic factors, especially human vascular endothelial growth factor (VEGF) (Hanahan & Folkman, 1996). Activation of angiogenic factors induces neovascularization, which is an important step for tumor progression and metastasis (Hanahan et al., 1996; Menakuru et al., 2008). VEGF blockade has demonstrated to have direct antitumor affect in human and animal cancer tumor cells by cutting the vascular supply and inhibiting endothelial proliferation. Several VEGF family members, VEGF-A through VEGF-E and placental growth factor (PIGF), have been identified in the human genome, among which most pro-angiogenic activity is mediated by VEGF-A (Zondor and Medina 2004). At least 9 pro-angiogenic VEGF isoforms are generated as a result of alternative splicing from a single gene, and $VEGF_{165}$, $VEGF_{121}$ and $VEGF_{121b}$ are the most abundant isoforms of VEGF (Ferrara et al, 2004).

Bevacizumab (AVASTIN®) is a recombinant humanized monoclonal antibody developed by Genentech used to inhibit VEGF that recognizes all isoforms of VEGF-A and thus inhibiting its biologic activity (Genentech Inc.2015). Bevacizumab became first angiogenesis inhibitor approved by FDA on February 26, 2004 for oncology use in the USA. Bevacizumab is approved for the treatment of multiple types of advanced/metastatic solid tumors including metastatic colorectal cancer (mCRC); First-line non-squamous non-small cell lung cancer (NSCLC); recurrent glioblastoma (GB); metastatic renal cell carcinoma (mRCC); persistent, recurrent, or metastatic carcinoma of the cervix; recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

TRS003 is developed as a proposed biosimilar product to the US-licensed reference product (RP), Avastin® (bevacizumab). Similar to US-licensed RP, TRS003 is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular

endothelial growth factor type A (VEGF-A). Through the neutralization of VEGF, angiogenesis required for the growth and persistence of solid tumors and their metastases is inhibited.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product", RP). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product specific nonclinical and clinical data.

Section 351(k) of the PHS Act defines the terms "biosimilar" or "biosimilarity" to describe that "the biological product is highly similar to the reference product not withstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." The analytical and nonclinical similarity assessments, as well as a pharmacokinetic similarity study performed were intended to evaluate analytical similarity and functional activity of TRS003, US-licensed RP and China-approved bevacizumab side-by-side to support the extrapolation to all of the US-licensed RP indications for which Teruisi is seeking licensure for TRS003.

1.2 RATIONAL OF THE STUDY

Teruisi has been successful in applying platform technology in a number of its programs for manufacturing monoclonal antibodies to facilitate process development and scale up. TRS003 cell line was developed by Destiny and vials of PCB were provided to Teruisi in 2015 for IND-enabling CMC development. Cell culture development platform comprises 3 phases including (1) media & feed screening performed in the shake flask, (2) process optimization taken place in the 3-L Bioreactor, process parameters such as seeding density, feed strategy, temperature, pH, DO, agitation speed, and sparge rate etc. are defined; key performance parameters such as productivity, growth and metabolite profile, and product quality (PQ) by Process Analytical Technology (PAT) are evaluated, and (3) scale up to the 200-L. Recovery process development employs a

standardized 3-column platform, consisting of MabSelect SuRe on Protein A Affinity, cation exchange in a bind and elute (B/E) mode, and anion exchange in a flow through mode. In addition, two orthogonal viral clearance steps, including a low-pH inactivation step and viral filtration step are included in the process to maximize product safety. A number of analytical assays have been developed to evaluate the product quality and safety. So far, four Drug Substance and four Drug Product lots have been manufacturing at 200 L scale for preclinical and clinical studies. The analytical 3-way similarity assessment results showed that TRS003 is similar to US-licensed Avastin and China-approved bevacizumab. A series of nonclinical studies have been conducted to evaluate and compare the pharmacological, pharmacokinetics and toxicological properties of the TRS003 and US-licensed RP, and China-approved bevacizumab. Comparable profiles of among TRS003, US-licensed RP, and China- approved bevacizumab have been observed in binding affinity, specificity and activity of Fab and Fc regions, in anti-tumor efficacy using xenograft models, and in PK and safety studies using cynomolgus monkeys.

1.3 PRECLINICAL STUDIES

Bevacizumab, the active ingredient of US-licensed Avastin®, is a recombinant humanized monoclonal immunoglobulin G1 subtype (IgG1) antibody targeting human vascular endothelial growth factor type A (VEGF-A). Bevacizumab binds with high affinity and selectivity to all known isoforms of soluble VEGF. The mechanism of action for bevacizumab across indications is neutralizing the biologic activity of VEGF protein through steric blockade of binding to its receptors VEGFR-1 (Flt-1) and VEGFR2 (KDR) on the surface of endothelial cells. Activation of VEGF receptors results in transduction signals that elicit mitogenic and pro-survival activity in vascular endothelial cells. Blockade of the VEGF/VEGFRs signaling pathway inhibits VEGF mediated angiogenesis, including that associated with tumor growth. VEGFR expression is very low or undetectable in most normal tissues (with the exception of renal glomeruli) but is significantly up-regulated in the vasculature of many solid tumors. The neutralization of VEGF by bevacizumab provides a relatively specific inhibition of tumor angiogenesis and thereby inhibition of tumor growth and metastasis.

TRS003 is a biological similar product for US-licensed Avastin® (bevacizumab). It has identical amino acid sequence as Avastin®. Following the FDA recommended stepwise approach,

comprehensive analytical similarity assessments were conducted and all the available *in vitro* data support that TRS003 has similar physicochemical primary structure, higher order structure, biological functions and Fc characteristics with the US-licensed Avastin® and China-approved bevacizumab. Additional nonclinical development studies have been conducted to evaluate and compare the dose-responsive pharmacological properties of the TRS003 and US- license Avastin and China-approved bevacizumab.

Functional testing focused on the mechanism of action, therefore, multiple assays interrogating Fab-mediated activities were conducted, including binding and neutralization of VEGF in HUVEC cell proliferation assay. The results from these assays confirmed that TRS003, US-license Avastin and China-approved bevacizumab have similar functional activities.

Fc functionality was included in the testing plan to assess Fc-binding activities and the structural integrity of the Fc domain. These induced comparative binding to multiple Fc receptors and the complement molecule C1q as well as lack of Fc-mediated effector function ADCC and CDC. There is no contribution of Fc receptor binding to the pharmacological activity and efficacy profile of TRS003, US- license Avastin and China-approved bevacizumab .

The PK study following a single intravenous (IV) administration of 1, 3 and 10 mg/kg of two lots of TRS003, one lot of US-licensed RP and one lot of China-approved bevacizumab were conducted in naïve Sprague-Dawley (SD) rats. Intravenous administration was chosen because it is the intended clinical administration route. SD rat is not a pharmacological relevant species; however, it is a sensitive test system to assess the primary and higher order structures (such as glycan structure of the antibody), as well as the structural integrity of the molecules. In addition, it can be used to detect potential off-target toxicity. In this study, no test article related adverse clinical effects were observed. All anti-VEGF antibodies were well tolerated. No difference was observed in serum concentration-time curves of the four lots of antibodies. This study demonstrated similar PK parameters after dosing of both TRS003,US-licensed RP and China-approved bevacizumab, confirming that similar exposures were achieved in SD rats after treatment with either TRS003, US-licensed and China- approved bevacizumab.

In summary, the analytical, pharmacological and PK similarity assessment results form the basis for the conclusion that TRS003 is similar to US-licensed RP and China-approved bevacizumab

and that TRS003 is expected to have similar clinical performance in all indications approved for US-licensed RP Refer to Investigator's Brochure for details).

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To assess pharmacokinetic (PK) similarity between TRS003, China-approved bevacizumab and US-licensed Avastin, as measured by $AUC_{0\text{-}inf}$ in healthy male subjects after a single 3 mg/kg dose.

2.2 SECONDARY OBJECTIVE

- To assess other PK parameters such as but not limited to C_{max}, AUC_{last} following a single dose of TRS003, China-approved bevacizumab and US-licensed Avastin in healthy male subjects.
- To determine the incidence of immunogenicity against TRS003, China-approved bevacizumab, and US-licensed Avastin in healthy male subjects.
- To evaluate the safety of TRS003, China-approved bevacizumab and US-licensed Avastin in healthy male subjects.

3 STUDY POPULATION AND SUBJECT ENROLLMENT

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria:

1. Healthy, male subjects, 18-55 years old with no significant medical history, and in good health as determined by detailed medical history, full physical examination, vital signs, 12-lead electrocardiogram (ECG), urinalysis and laboratory tests at screening.
2. Body mass index of 17.5-30.5 kg/m^2 and body weight of 50-95 kg.
3. Protocol-specified hematology, coagulation, blood chemistry and urinalysis within the laboratory normal range at screening, unless deemed not clinically significant by the Investigator.
4. Subjects must have adequate organ function according to the following laboratory values:
    a. Bone marrow function (absolute neutrophil count ≥1500/mm^3 and platelet count ≥100,000/mm^3)
    b. Adequate liver function [alanine aminotransferase (ALT) ≤3 × upper limit normal (ULN) and alkaline phosphatase ≤2 × ULN, total bilirubin ≤1.5 mg/dL]
    c. Adequate renal function creatinine clearance ≥60 mL/min based on Cockcroft-Gault equation.
5. Subjects must agree to use an acceptable form of birth control throughout the study and for at least 18 weeks after the study is over.

3.1.2 Exclusion Criteria:

1. Subjects unable to give voluntary informed consent.
2. Evidence or history of clinically significant disease, cancer other than adequately treated basal cell or squamous cell carcinoma of the skin.
3. Subjects on anticoagulant drugs, anemic or with known bleeding diatheses.
4. Subjects with a history of severe, uncontrolled hypertension, heart disease, cerebrovascular incidents, gastrointestinal bleeding, hemoptysis, frequent epistaxis or gingival bleeding.
5. History clinically significant orthostatic hypotension, fainting spells, vasovagal syncope.
6. Uncontrolled severe hypertension (140/90 mm Hg).

7. Previous treatment with an anti-VEGF antibody or any other antibody or protein targeting the VEGF receptor.
8. Use of any prescription, investigational drugs, herbal supplements or nonprescription drugs within 1 month or 5 half-lives (whichever is longer) prior to the first dose, or dietary supplements within 1 week prior to the first dose. If needed, paracetamol/acetaminophen may be used, but must be documented in the Concomitant medications/Significant non-drug therapies page of the CRF.
9. Serious unhealed wound, cutaneous ulcer or bone fracture at the time of screening.
10. Major surgery or major dental procedure or significant traumatic injury within 2 months prior to screening, or any planned surgery or procedure within 3 months after investigational treatment administration. Subjects must have recovered from all acute surgery- or trauma-related complications.
11. Subject's medical and family history of recent or recurrent thromboembolism or other clotting and coagulation disorders.
12. Donated blood over 400 mL within 3 months.
13. History of relevant and clinically significant intra-abdominal inflammation, gastrointestinal perforation or gall bladder perforation.
14. History of severe allergic or anaphylactic reaction to a therapeutic drug or severe seasonal allergies.
15. Recent (within the last three [3] years) and/or recurrent history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
16. A positive hepatitis B, hepatitis C or HIV tests at screening indicative of a current or past infection.
17. Current use of tobacco or nicotine-containing products. Concomitant treatment was given only if Investigator believes strictly necessary and should be documented.
18. Current use of any biologic drugs.

3.2 LIFESTYLE CONSIDERATIONS

3.2.1 Meals and Dietary Restrictions

Subjects will receive a standard diet whilst resident in the clinical center.

3.2.2 Alcohol

Refrain from intake of alcoholic beverages from 48 hours prior to study treatment administration until Day 8 postdose. After Day 8, subjects are discouraged from consuming alcohol until the completion of the study, but may consume no more than 1 unit of alcohol per day.

3.2.3 Activity

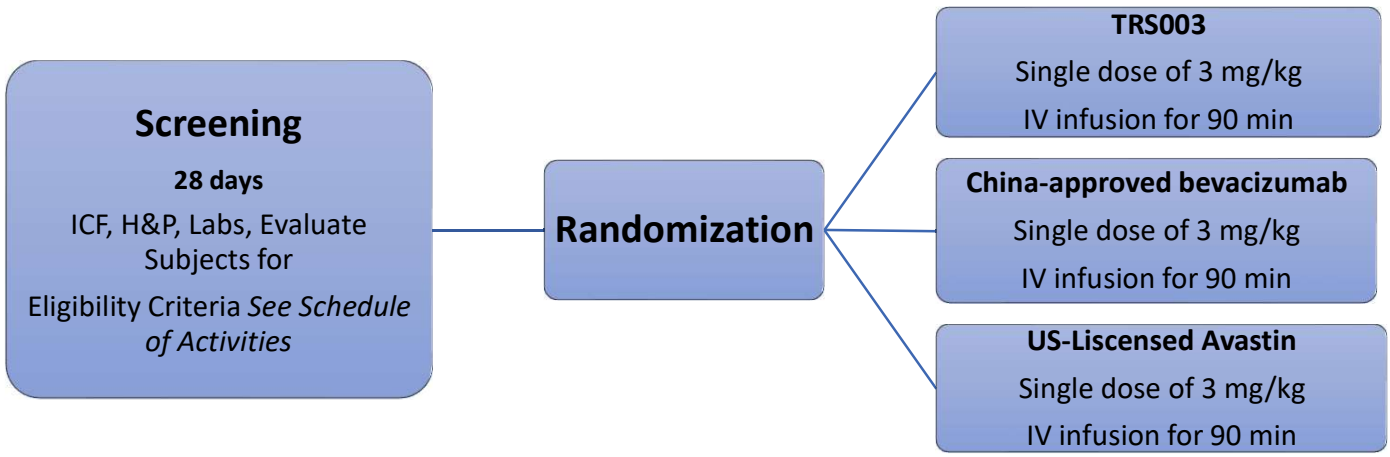
Subjects will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during the study (eg, watching television, reading).

Subjects should refrain from strenuous exercise for 48 hours before the Day -1 and admission to the clinical center and throughout the study.

Subjects will be advised not to donate blood or plasma donation for at least 3 months after the last dose administration.

3.3 OVERALL STUDY DESIGN

Study Schema



From dosing until End of Study (EOS)-12 weeks

PK & ADA Sampling

Safety labs, H&P see Schedule of Activities

This is a 12-week, randomized, double-blind, single-dose PK study. Approximately 114 healthy male subjects (screening occurred within 28 days prior to dosing) will be randomized 1:1:1 to either TRS003, China-approved bevacizumab or US-licensed Avastin groups. Study drug will be dispensed as a single 3 mg/kg dose IV infusion within 90 minutes. PK and immunogenicity samples will be collected and safety will be assessed.

3.4 DOSE SELECTION RATIONAL

Based on PK of bevacizumab, healthy subjects provide more homogenous population with less PK variability compared to those of cancer patient population. Due to the potential risk of ovarian failure, male healthy subjects are selected for the proposed PK similarity study.

The approved therapeutic dose of Avastin are between 5 and 15 mg/kg given Q2W or Q3W. The 3 mg/kg was chosen based on the PK linearity of bevacizumab at dose of 1-20 mg/kg and the high analytical sensitivity for the determination of bevacizumab concentrations at lower dose ranges. A dose of 3 mg/kg of study drug is not expected to pose a significant risk to healthy subjects.

The 90-minute IV infusion is consistent with US-licensed Avastin prescribing information.

3.5 SCREENING VISIT

Potential subject will be scheduled for a screening visit. Screening procedures will take place on the Clinical Research Center.

Prior to participation in the study, all volunteers will have a routine history and physical along with screening blood tests weight, height and vitals obtained at the screening visit. In this proposed application, all subjects will have a baseline 12 lead ECG to exclude cardiovascular disease before entering the study. Subject's current medication schedule will be reviewed to ensure subjects safety during the treatment (Refer to **Table 1** for details).

After all the screening results are obtained eligibility criteria will be reviewed and a complete clinical evaluation will be performed. All screening assessments will occur within 28 days prior to the study drug admission.

If an assessment was performed as part of the subject's routine clinical evaluation and not specifically for this study, it needs not be repeated after signed ICF has been obtained. However, the assessments must fulfill the study requirements and should be performed within the specified timeframe prior to the study drug administration. If hematology and serum chemistry labs were obtained ≥3 weeks as indicated in Schedule of Activities the laboratory evaluations need to be repeated within 72 hours prior dosing. Retesting of abnormal screening values that lead to exclusion are allowed only once during the Screening Phase (to reassess eligibility). The last result obtained prior to dosing with study drug will be used to determine eligibility.

The prospective subject's medical history will be assessed prior to the drug administration. During the study period, AEs will be evaluated with each outpatient visit. The recent medical history assessment will include recent medication changes including over the counter medications or supplements.

3.6 RANDOMIZATION AND BLINDING

Subjects in each clinical site will be 1:1:1 randomized prior to dosing using a computer-generated randomization schedule to receive either TRS003, US-licensed Avastin or China-approved bevacizumab.

Both the principal investigator and subject will be blinded as to whether a subject is receiving TRS003, US-licensed Avastin or China-approved bevacizumab. A designated person in the Investigational Pharmacy will dispense the appropriate drug accordingly.

Each vial administered to subjects will have a unique code, and quick unblinding will be performed by Investigational Drug Pharmacy, the principal investigator, or the sponsor should a medical emergency arise for a participant. Upon completion of the study participation, all subjects will be unblinded.

3.7 CONFINEMENT PERIOD

This is randomized, double-blind, single-dose, three-arm, parallel-group, phase 1 study to compare pharmacokinetic and safety of TRS003 to China-approved bevacizumab and US-licensed Avastin, when administered intravenously to healthy male subjects. If safety labs are

≥ 3 weeks, safety laboratory assessments should be repeated within 72 hours (-Day1) before the drug administration. Additionally, vital signs, medication history, physical exam will be done on -Day1 and eligibility will be re-evaluated after the repeat laboratory assessments results are received. Subject will visit the clinical research site in the Day-1 admission and will stay at the unit 24 hour after the drug administration. Dose should be calculated based on the most recent weight.

All drug administrations will be performed in the clinical center under the supervision of appropriately trained staff. Subjects will stay at the clinical unit for at least 24 hours after dosing for PK and safety assessment. After 24 hours subject will be followed until the Day 85 (12 Weeks) as an outpatient (Refer to the **Table 1** and **Table 2**).

3.8 DURATION OF TREATMENT

The duration of this study will be 16 weeks (28-day screening period and 12-week post-dose assessment). Subjects will be followed until the Day 85 (12 Weeks) following the single dose of the study drug (Refer to the **Table 1**).

3.9 OUTPATIENT VISITS

For outpatient visits and procedures see Schedule of Activities (**Table 1** and **Table 2**). On days 3, 5, 8, 15, 29, 43, 57, 71, 85 days after the study drug administration, subjects will return to undergo the assessments outlined in the Schedule of Activities. Subjects will receive physical examination, will be evaluated for vital signs and AEs. Additionally, during these visits blood samples will be obtained for safety labs, PK and ADA samples (Refer to **Table 1** and **Table 2**)

3.10 END OF STUDY (EOS) VISIT

At the EOS safety labs and assessments are evaluated (Refer to **Table 1** and **Table 2**).

4 STUDY DRUG AND TREATMENT ALLOCATIONS

4.1 TREATMENT COMPLIANCE

The site will maintain accurate dosage preparation records and should ensure that all pertinent/required information on the preparation and administration of the dose is captured.

The details of drug administration will be recorded in the CRF. Upon termination of the study, or at the request of the sponsor, the pharmacist must return the study drugs to Sponsor, unless it is destroyed at the site as agreed upon by both the sponsor and the site.

4.2 STUDY DRUG DESCRIPTION, STORAGE AND HANDLING

TRS003 developed as a proposed biosimilar of bevacizumab (Avastin®, Genentech), TRS003 is a recombinant humanized $IgG_{1\kappa}$ monoclonal antibody (mAb) targeting vascular endothelial growth factor (VEGF), a critical angiogenic factor involved in both physiological and pathological conditions. There are several isoforms of VEGF that are encoded by a single gene. The isoforms include placental growth factor and VEGF-A through VEGF-E. Most pro-angiogenic activity is mediated by VEGF-A. Like bevacizumab, TRS003 molecule binds VEGF-A and prevents VEGF-A from binding to its cell surface receptor VEGFR2, ultimately resulting in an inhibition of angiogenesis.

TRS003 is composed of two identical heavy chains of 49,713 Da each, and two identical light chains of 23,447 Da each. The predominant glycan moiety of TRS003 is N-linked typical core fucosylated biantennary glycan with 0, 1 or 2 terminal galactose residues attached to each heavy chain at Asn-303 in the Fc region. The average size of the N-linked oligosaccharide moiety is approximately 1,500 Da per heavy chain.

The TRS003 drug substance is formulated at 25 mg/mL in 5.8 mg/mL sodium phosphate (monobasic, monohydrate), 1.2 mg/mL sodium phosphate (dibasic, anhydrous), 60 mg/mL α,α-trehalose dihydrate, 0.4 mg/mL polysorbate 20, pH 6.2. The formulated TRS003 drug substance (DS) and TRS03 drug product (DP; 100 mg/vial) is a clear to opalescent, colorless to slightly brown liquid that is essentially free of visible particles.

The TRS003 drug product is a sterile solution for intravenous infusion consisting of 4 mL of TRS003 drug substance that is filled into single-use Type I glass vials capped with butyl stopper.

US licensed AVASTIN vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2−8°C (36−46°F). Avastin vials should be protected from light. Do not freeze or shake. Avastin is a clear to slightly opalescent, colorless to pale brown solution in single-dose vials. Diluted Avastin solutions may be stored at 2−8°C (36−46°F) for up to 8hours. Store in the original carton until time of use. No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

China-approved bevacizumab is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of Bevacizumab (25 mg/mL). The product is formulated in α,α-trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate 20, and Water for Injection. Bevacizumab Injection for intravenous use is a sterile, clear to slightly opalescent, colorless to pale brown solution, with pH of 5.9~6.3.

4.3 DRUG ADMINISTRATION

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw necessary amount of TRS003/China--approved bevacizumab or US licensed Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion within 90 minutes the dose of 3 mg/kg.

TRS003/ China-approved bevacizumab/US-licensed Avastin administration should be completed within 4 hours at room temperature after dilution or within 8 hours at 2-8℃ after dilution. This ensures sufficient time for healthcare professionals to conduct the drug preparation and administration.

4.4 SPECIAL PRECAUTIONS AND CLINICAL INTERVENTIONS

Participants will receive only a single dose of 3mg/kg of TRS003, China-approved bevacizumab or US-licensed Avastin, thus it is unlikely that this treatment will cause any major AEs characteristic for bevacizumab.

4.4.1 Infusion Reactions

All therapeutic monoclonal antibodies (mAbs) used for cancer treatment have the potential to cause infusion reactions. Symptoms vary with a wide spectrum of severity, ranging from mild fever and chills to life-threatening anaphylaxis with bronchospasm, and hypotension. Typically, infusion reactions to monoclonal antibodies develop within 30-120 minutes after the initiation of drug infusion, although symptoms may not show up until 24 hours. The majority of reactions occur after the first or second exposure to drug, although it can also occur during subsequent treatments. Infusion reactions (e.g., hypertension, hypertensive crisis, wheezing, oxygen desaturation) and hypersensitivity [including anaphylactic/anaphylactoid reactions], chest pain, rigors, headache, diaphoresis) may occur with the first infusion (uncommon). Stop infusion in patients experiencing severe infusion reactions and administer appropriate therapy.

To date there is no data that suggest that routine premedication or reinstitution of therapy in patients with previous severe infusion reactions prevents these infusion reactions. However, premedication can help to reduce the severity of infusion reaction but anaphylaxis cannot be prevented by premedication. Thus, following supplies and equipment needs to be readily in any area where chemotherapy is administered: IV fluids, epinephrine, antihistamines, oxygen, aerosolized bronchodilators, intubation and tracheostomy equipment, and a defibrillator.

Infusion reactions are classified according to NCI CTCAE Grading.

Table 3 Management of Infusion-Related Reactions/Hypersensitivity Reactions (NCI CTCAE Grade)

Grade 1 Mild transient reaction; infusion interruption NOT indicated; intervention NOT indicated	• Monitor subject closely until recovery from symptoms, Consider premedication with 50 mg diphenhydramine or 650 mg acetaminophen at least 30 minutes before additional study drug administration
Grade 2 Cessation of infusion or therapy is indicated. Responds promptly to symptomatic treatment.	• Stop infusion; start IV saline infusion; IV **50 mg diphenhydramine or 650 mg acetaminophen**; depending on symptoms, consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms • Restart infusion at 50% of initial rate: if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. • Prophylactic medication indicated for less than or equal to 24 hours • Symptoms recur: stop and discontinue further treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
Grade 3-4 Prolonged recurrence of symptoms, hospitalization indicated for other clinical sequelae, maybe life threatening and hospitalization may require. Should discontinuation from treatment	• Stop infusion; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. • Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (for example, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

4.4.2 Extravasation

In the event of extravasation, infusion should be stopped immediately and the investigator needs to be consulted immediately. Treatment of extravasation should follow local standard of care.

4.5 WARNINGS AND PRECAUTIONS OF BEVACIZUMAB

GI fistula and intraabdominal abscess formation have been observed to be higher incidence in patients receiving Avastin products during metastatic CRC and ovarian cancer. Avastin treated cervical cancer patients also had higher incidence of gastrointestinal-vaginal fistulas, who may also develop bowel obstruction and require surgical intervention.

Most Common non-GI fistulas associated with Avastin were tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder fistulas occurring within the 6 months of Avastin treatment.

Avastin impairs the wound healing in animal models, thus administration of Avastin should be avoided at least 28 days before and after surgery.

Arterial and venous thromboembolic effects were also associated with Avastin use. Avastin should not be administered to subjects with a >Grade 3 arteria and venous thromboembolic (ATE/VTE).

Avastin also increases ovarian failure incidence is premenopausal females.

Additionally, Avastin can also affect following system organ class (SOC): cardiovascular (hypertension/hypotension, venous thromboembolism, peripheral edema, arterial thrombosis), CNS (headaches, fatigue, dizziness, peripheral sensory neuropathy, anxiety, myasthenia gravis), endocrine and metabolic (ovarian failure, hyperglycemia, hypomagnesemia, weight loss, hyponatremia, hypocalcemia, hypoalbuminemia), dermatologic (exfoliative dermatitis, xeroderma, alopecia)

(Refer to Avastin label for details about warnings and precautions)

4.6 CONTRAINDICATIONS

Hypersensitivity to bevacizumab, any component of the formulation, Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

4.7 PROTOCOL THERAPY AND OFF STUDY CRITERIA

Participation in this research study is completely voluntary. Subjects are free to withdraw from this study at any time by informing the PI or one of the co-investigators. If a subject, for whatever reason, no longer meets the inclusion or exclusion criteria, they will be notified and withdrawn from the study. Furthermore, if the volunteer is noncompliant they will be withdrawn from the study and another matched volunteer will be recruited to take their place.

Additionally, prior to removal from study, effort must be made to have all subjects complete at least 1 outpatient visit that involves safety labs.

4.7.1 Criteria for removal from protocol therapy:

- Completion of protocol therapy
- Participant requests to be withdrawn from the study
- Investigator discretion
- Lost to follow-up or noncompliance
- AEs or safety concerns by Investigator or Sponsor

4.7.2 Off Study Criteria

Once a subject is taken off study, no further data can be collected.

- Completed study D85-oupatient visit
- Participant requests to be withdrawn from study
- Subject during outpatient visit period
- Death or serious side effects
- Screen failure

4.7.3 Subject Replacement

Subjects who do not receive the full dose of study drug, or who withdraw from the study or with significant protocol violations may be replaced at the discretion of the investigator after informing the Sponsor.

4.8 STUDY CLOSURE

The investigator may terminate the study at any time in the interest of subject welfare. The sponsor may terminate the study prematurely at any time. Reasons for the closure of an investigational site or termination of a study may include:

- The Investigator fails to comply with the protocol or ICH/GCP guidelines
- Safety concerns
- Inadequate recruitment of subjects by the investigator
- Completion of the study

If the clinical study is prematurely terminated or suspended, the sponsor or CRO representative will inform the investigator and the regulatory authorities of the termination/ suspension and the reasons for the termination/suspension as appropriate. The investigator should promptly notify the IEC/IRB of the termination or suspension and provide reasons. The sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause.

Premature termination of the study by either PI or sponsor will be governed under the terms of the contract between both parties.

5 STUDY ASSESTMENTS AND EVALUATIONS

5.1 BLOOD SAMPLES FOR PK EVALUATIONS

Blood samples will be collected from all subjects to determine the serum concentration of TRS003/China-approved bevacizumab and US- licensed Avastin using a validated immunoassay for PK analyses. PK samples will be collected at multiple timepoints throughout the study (Refer to **Table 1**).

Approximately 6 ml blood will be collected at each of the following time points. Serum will be separated and stored for bioanalysis of TRS003//China-approved bevacizumab and US-licensed Avastin concentration with a validated assay.

5.2 BLOOD SAMPLES FOR IMMUNOGENICITY EVALUATIONS

Immunogenicity samples will be collected at multiple timepoints throughout the study after the end of infusion (Refer to **Table 1**). If a sample is positive in the screening assay, a confirmatory assay will be conducted. If a confirmatory assay is positive, the titer and the neutralization activity will be tested.

Teruisi is conducting the assay validation for PK and anti-drug antibody (ADA) assays according to FDA Guidance, “Bioanalytical Method Validation May 2013”.

Approximately 8 ml blood will be collected and serum will be separated and stored for bioanalysis of anti-TRS003 antibodies with validated assays. The incidence of antibodies against TRS003 will be summarized for all subjects who received investigational drug.

5.3 SAFETY ASSESSMENTS

Safety will be assessed by periodic physical examination findings, vital signs, clinical laboratory tests, 12-lead ECGs, and AEs (Refer to **Table 1**). All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and association with the study drug. Clinical laboratory parameters, vital signs, and ECG parameters will be listed and summarized using descriptive statistics. The number and percentage of subjects testing positive for ADAs will be summarized by treatment and time point.

5.4 CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

6 DATA COLLECTION AND MANAGEMENT

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Hardcopies of the study visit worksheets will be used as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. All source documents should be completed in a legible manner to ensure accurate interpretation of data.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into EDC system, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Only individuals who have received training on the EDC are allowed to make eCRF entries, corrections, and alterations. Training must be documented and a log of all EDC users and their rights within the system must be maintained. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct.

Any outstanding entries must be completed immediately upon notice. No blank sections should be left on CRF and explanations has to be recorded for all missing data. All source documents should be retained. All essential documents should only contain subject coded identifiers and no personal identifying information should be transmitted.

6.1 STUDY RECORD RETENTIONS

After completion of the study and when all collected data are validated, the database will be locked, pursuant to the prior approval by the Sponsor (or its designee). Final data will be extracted from the EDC system and delivered in the form of SAS® datasets. A Portable Document Format (PDF) copy of the eCRF will be produced for each study subject and included in the final delivery.

All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with sponsors/CROs security standards. Each Subject will have identifiers that will be kept at the study sites.

If clinical site/sponsor becomes aware of loss or destruction of data due to a major breach occurrence that has jeopardized subject confidentiality and trial data, the IRB will be notified.

Study documents should be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

6.2 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, study manuals, or ICH GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and if applicable, in eCRFs and study reports, in coordination with the sponsor or their designated CRO. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the requirements of the reviewing IRB.

6.3 PUBLICATION AND DATA SHARING

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee.

7 HUMAN SUBJECT PROTECTION AND REGULATORY OVERSIGHT

7.1 INFORMED CONSENT PROCESSES AND DOCUMENTATION

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written ICFs and any other written information to be provided to the participants. Participants will be asked to read and review IRB-approved ICFs and other written information. ICF should include detailed description of study procedures, risk and benefits, directions, participant's rights, compensation if applicable, and contact of Human Subject Protection Services. Additionally, investigator will explain the research study to the participant in terms suited to the participant's comprehension and answer any questions that may arise. Investigator should explain their rights as research participants, study procedures, risk and benefits, anticipated adverse effects. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. ICF should be signed prior to any interventions for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participant will be given a copy of the signed consent form and the original consent form will be kept as a permanent record.

7.2 CONFIDENTIALITY AND PRIVACY

Participant's identification is concealed and a number is used as the identifier instead of the subject's name. The principal investigator, co-investigators will have the list of study subjects' names as they correlate with the study number. Only some of the research staff involved with the study will have access to data. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor

8 SAFETY REPORTING

8.1 DEFINITIONS

An adverse (AE) event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial whether or not the event is considered related to the treatment or clinically significant.

For this clinical trial, AEs will include any events reported by the subject, any new medical conditions, symptoms, any new abnormal findings on physical examination or laboratory evaluation. Additionally, any worsening of a pre-existing condition or abnormality will also be considered as an AE.

All AEs must be recorded on eCRF. All AEs must be followed return to baseline or stabilizes.

Serious adverse events (SAE):

A serious adverse event is defined as any adverse experience that meets any of the following criteria:

- Results in death;
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization. Additionally, complications occurring during hospitalization are also considered AEs.
- Results in persistent or significant disability or incapacity (This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.);
- 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.

Adverse Reaction

Any AE caused by a drug.

8.2 CAUSALITY OF AES

Causality assessment has become a common routine procedure in pharmacovigilance. Causality assessments can decrease disagreement between assessors, classify relationship likelihood and improvement of scientific evaluation.

- Limitations of causality assessment are following:
- It can NOT assess accurate quantitative measurement of relationship likelihood
- It can NOT distinguish valid from invalid cases
- It can NOT prove the connection between drug and event
- It can NOT quantify the contribution of a drug to the development of an adverse event

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the 2 categories below. In a clinical trial, the study product must always be suspect.

Related: The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related: There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Protocol Deviation

Any change, divergence, or departure from the IRB-approved research protocol.

Non-compliance

The failure to comply with applicable Human Research Protections Program policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; AND

- Is related or possibly related to participation in the research; AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3 CATEGORIZATION OF AEs

All AEs and clinically significant laboratory abnormalities will be graded according to Common Terminology Criteria for AEs, Version 4.03 dated 14 June 2010. For any term that is not specifically listed on the CTCAE scale, intensity will be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

8.4 REPORTING OF SAEs AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARs)

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported by investigator to the sponsor within 24 hours (and IRB as required) of first becoming aware of the SAE. The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In

addition, the sponsor must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting

SAEs will be collected by the investigator from day 1 through 85 days after the last dose of study medication. SAEs that occur within 85 days following the drug administration, must also be reported within the same timeframe. Any SAE that is judged by the investigator to be related to the study medication must be reported regardless of the amount of time since the drug administration. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor (or its designee) within 24 hours of receipt by the investigator. All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible. To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and clinical laboratory reports should be obtained.

8.5 IRB REPORTING

The investigators will report to the IRB the following according to the requirements of reviewing IRB:

- All SAEs
- Non-compliance to GCP or protocol deviations as required by IRB

IND Safety Reports and any unexpected incidences or problems during the trial may be also reportable to the IRB as per IRB requirement.

8.6 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented to assure that any missing data will be communicated with sites for clarification and resolution.

Standard Operating Procedures (SOPs) should be available to monitors. Monitors will verify that all the clinical trial procedures are conducted, documented and reported in compliance with the protocol, ICH, GCP, GLP, GMP and other applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

8.7 CLINICAL MONITORING PLAN

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Details of clinical site monitoring will be documented in a separate Study Monitoring Plan (SMP). The SMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. In general monitoring visits would include pre-study visits (to qualify the site and investigators), study initiation visit, interim visits at appropriate frequency based on recruitment speed and need to clean data for dose-escalation decisions, and study closeout visits after database lock.

Independent audits may be conducted by the sponsor to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the SMP.

Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct

A monitor(s)/sponsor representative(s) will meet with the investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording study data. After enrollment of the first subject, a monitor(s)/sponsor representative(s) will be assigned to periodically monitor each investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) and/or ICH guidelines were followed.

The investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed CRFs, signed consent forms and other study related documents are readily available for review.

As a sponsor for clinical trials, FDA regulations require the Investigators to facilitate monitoring process. Monitors will evaluate adherence to the protocol, regulations, SOPs, human subject protection, study data, specifically data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

9 STATISTICAL CONSIDERATIONS

9.1 GENERAL STATISTICAL CONSIDERATIONS

Descriptive statistics will be utilized for all safety, efficacy, immunogenicity, and pharmacokinetic parameters. Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. All data collected will be presented in subject listings.

9.2 PHARMACOKINETIC ANALYSIS

Serum drug concentration-time data will be analyzed by standard non-compartmental methods. The PK parameters will include maximum drug concentration (C_{max}) and AUC_{last}, clearance (CL), terminal half-life ($t_{1/2}$), and volume distribution at steady state (V_{ss}). Descriptive statistics of PK parameters (geometric mean, CV%, arithmetic mean, median, SD, minimum and maximum) will be provided.

The primary assessment of 3-way PK similarity (3 pairwise comparison) will be based upon a 90% confidence interval (CI) for the ratio of the geometric means (TRS003 versus China-approved bevacizumab, TRS003 versus US-licensed Avastin, and US-licensed Avastin versus China-approved bevacizumab) for $AUC_{0\text{-}inf}$ on the PK analysis set. If the 90% CI of the ratio of the geometric means for $AUC_{0\text{-}inf}$ is within the range of 80-125%, then PK similarity will be concluded. If there are multiple study sites, the significance of clinical sites will also be tested and may be included into the final statistical model.

Secondary PK parameters such as but not limited to C_{max}, AUC_{last} will be analyzed using the same statistical approach. A nonparametric approach, for example, Wilcoxon signed-rank test, will be taken to evaluate parameters such as $t_{1/2}$. Exploratory analyses may be performed for other PK parameters as deemed appropriate.

9.3 IMMUNOGENICITY ANALYSIS

All samples will first be analyzed for ADAs in a screening assay. Study samples with results below the screening cut-off will be reported as negative for ADAs. In the event of a positive

result in the screening assay, samples will be analyzed in the confirmatory assay. The incidence of ADA will be summarized for all subjects who received at least one administration of investigational drugs. Impact of ADAs on PK and safety of investigational drug will be evaluated, if applicable.

9.4 DETERMINATION OF SAMPLE SIZE

Assuming a CV of 20% (Knight et al., 2016) in male healthy subjects and 1.05 for the geometric mean ratio of $AUC_{0\text{-}inf}$, the study with 29 evaluable subjects per arm will have 95% power to demonstrate the PK similarity between TRS003/China approved bevacizumab and US-licensed Avastin (90% CI of geometric mean ratio within 80-125%). Assuming a 15% drop out rate (including non-evaluable subjects) and a 95% power, approximately 114 subjects (38 per arm) will be randomized in 1:1:1 ratio.

Note: 80%, 85%, 90%, and 95% power corresponding to a sample size of 18/arm, 20/arm, 23/arm, and 29/arm, respectively.

9.5 POPULATION ANALYSIS

9.5.1 Safety Population Analysis

Safety population consists of all subjects who received the investigational product.

9.5.2 PK Population Analysis

PK population consists of all subjects who have evaluable concentration-time data.

9.6 SAFETY ANALYSIS

Any subject receiving investigational drug will be included in the summaries and listings of safety data. Safety and tolerability profile will be characterized by following criteria:

- Relationship of study therapy and laboratory abnormalities.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

Safety will be assessed by periodic physical examination findings, vital signs, clinical laboratory tests, 12-lead ECGs, and AEs (Refer to **Table 1**). All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and association with the study drugs. Clinical laboratory parameters, vital signs, and ECG parameters will be listed and summarized using descriptive statistics. The number and percentage of subjects testing positive for ADAs will be summarized by treatment and time point.

9.7 TABULATION OF INDIVIDUAL PARTICIPATION DATA

Data tabulations will summarize the following subject numbers:

- Enrolled
- Investigational drug treatment dose received
- Evaluable for safety
- Protocol violations
- Protocol completions
- Withdraw from study due to:
  - Withdrew consent
  - Lost to Follow-up

10 REFERENCES

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