Clinical Study Protocol

# A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Bevacizumab (CT-P16, EU-approved Avastin and US-licensed Avastin) in Healthy Male Subjects

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| **Sponsor:** | CELLTRION, Inc.<br>23, Academy-ro,<br>Yeonsu-gu, Incheon<br>22014 Republic of Korea |
| **Clinical Research Organization:** | [redacted] |
| **Principal Investigator:** | [redacted] |
| **Sponsor Protocol No.:** | CT-P16 1.1 |
| **IMP Name:** | CT-P16 |
| **Development Phase:** | Phase I |
| **Date of Protocol:** | 07 June 2017 |
| **Version of Protocol** | 1.0 |

# SIGNATURE PAGE

**Declaration of Sponsor or Responsible Medical Expert**

**Protocol Title: A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety of Three Formulations of Bevacizumab (CT-P16, EU-approved Avastin and US-licensed Avastin) in Healthy Male Subjects**

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (WMA 2013), and the guidelines on Good Clinical Practices (GCP) applicable to this clinical study.

**Sponsor Signatory/Responsible Medical Expert**

[redacted]
CELLTRION, Inc.

Date

# SIGNATURE PAGE

**Declaration of the Principal Investigator**

**Protocol Title: A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics, Safety of Three Formulations of Bevacizumab (CT-P16, EU-approved Avastin and US-licensed Avastin) in Healthy Male Subjects**

I have read and understand all sections of the protocol entitled "A Randomized, Double-blind, Three-arm, _Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Bevacizumab (CT-P16, EU-approved Avastin and US-licensed Avastin) in Healthy Male Subjects" and the accompanying current investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the [redacted], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use harmonised tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

**Principal Investigator**

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| Signature of Principal Investigator | Date |
| Printed Name of Principal Investigator | |

# PROTOCOL SYNOPSIS

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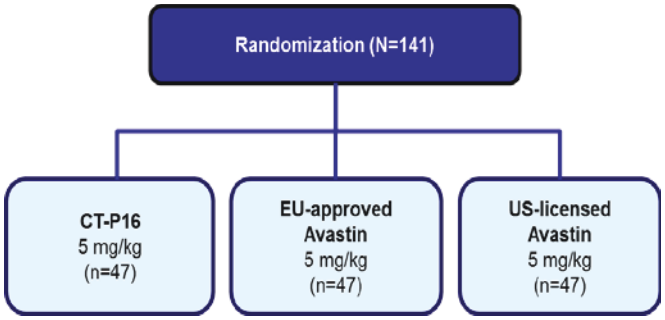
| **Title:** | A Randomized, Double-blind, Three-arm, Parallel Group, Single-dose Study to Compare the Pharmacokinetics and Safety of Three Formulations of Bevacizumab (CT-P16, EU-approved Avastin and US-licensed Avastin) in Healthy Male Subjects |
| **Protocol Number:** | CT-P16 1.1 |
| **Development Phase:** | Phase I |
| **Sponsor:** | CELLTRION, Inc. |
| **Principal Investigator:** | [redacted] |
| **Study Center(s):** | Approximately 3 sites |
| **Study Objective(s):** | **Primary objective**<br>• To demonstrate the similarity of the pharmacokinetics (PK) in terms of area under the concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$), AUC from zero to the last quantifiable concentration ($AUC_{0\text{-}last}$) and maximum serum concentration ($C_{max}$) of CT-P16, United States (US)-licensed Avastin and European Union (EU)-approved Avastin in healthy male subjects (CT-P16 to EU-approved Avastin, CT-P16 to US-licensed Avastin, and EU-approved Avastin to US-licensed Avastin).<br><br>**Secondary objectives**<br>• To assess the additional PK parameters of CT-P16, US-licensed Avastin and EU-approved Avastin in healthy male subjects.<br>• To evaluate the safety and immunogenicity of CT-P16, US-licensed Avastin and EU-approved Avastin in healthy male subjects. |
| **Study Design:** | This study is a double-blind, three-arm, parallel group, single-dose study. A total of 141 subjects will be enrolled; 47 subjects in each of the 3 arms of the clinical study.<br>In each arm, all subjects will receive a single dose (5 mg/kg) of either CT-P16, EU-approved Avastin, or US-licensed Avastin by intravenous (IV) infusion for 90 min (±5 min) on Day 1 followed by 15 weeks during which the PK, safety, and immunogenicity measurements will be made. The randomization will be stratified by body weight (<70 kg vs ≥70 kg) assessed on Day-1 and site.<br>  <br>**Figure 1. Study schema** |
| **Investigational Medicinal Product(s) (IMP):** | **Test Investigational Product, Dose and Route of Administration:**<br>• CT-P16: 5 mg/kg, intravenous infusion for 90 min (±5 min)<br>**Reference Investigational Products, Doses and Routes of Administration:**<br>• EU-approved Avastin: 5 mg/kg, intravenous infusion for 90 min (±5 min)<br>• US-licensed Avastin: 5 mg/kg, intravenous infusion for 90 min (±5 min) |
| **Number of Subjects:** | A total of 141 subjects will be enrolled in the clinical trial and randomized (1:1:1) into 3 study arms as follows:<br>• Arm 1 (n=47) CT-P16 |

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| | • Arm 2 (n=47) EU-approved Avastin<br>• Arm 3 (n=47) US-licensed Avastin |
| **Study Population:** | Healthy male subjects, 19 to 55 years of age with a body weight of ≥ 50 kg and a body mass index between 18.0 and 29.9 kg/m$^2$ (both inclusive) are planned for enrollment. |
| **Inclusion and Exclusion Criteria** | **Inclusion Criteria**<br>Subjects who meet the following criteria will be considered eligible to participate in the clinical study:<br>1. Subject is able to understand and to comply with protocol requirements, instructions, and restrictions.<br>2. Subject voluntarily agrees to participate in this study and has given a written informed consent prior to performing any of the screening procedures.<br>3. Healthy male subjects between the ages of 19 and 55 years, both inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure [BP] and heart rate [HR] measurement, 12-lead electrocardiogram [ECG] and clinical laboratory tests prior to the administration of investigational medicinal product [IMP]).<br>4. Body Mass Index (BMI) between 18.0 and 29.9 kg/m$^2$ (both inclusive) and a body weight ≥ 50 kg.<br>5. Male subject, unless surgically sterile for at least 6 months before the time of the administration of the IMP, must be willing to abstain from sexual intercourse or willing to use a condom in addition to having his female partner of childbearing potential use an additional form of contraception such as an intra-uterine device, barrier method with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant from Day 1 until at least 6 months after the administration of the IMP. The female partner of the participating subject should be familiar with the use of the respective contraceptive methods. Intra-uterine devices and hormonal methods for contraceptive should have been used for at least one menstruation cycle before infusion.<br><br>**Exclusion Criteria**<br>Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:<br>1. Subject is a female.<br>2. Subject has a medical history of disease including one or more of the following(s):<br>- Clinically significant allergic reactions (spontaneous, atopic allergy, or following drug administration) such as asthma, urticaria, angio-oedema, and eczematous dermatitis, hypersensitivity, also including known or suspected clinically relevant drug hypersensitivity to benzyl alcohol or any components of the test and reference IMP formulation or other similar drugs.<br>- Cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anaemia or blood dyscrasia), metabolic (including known diabetes mellitus), neurologic or pulmonary diseases classed as significant by the Investigator.<br>- Non-healing wound, ulcer, bone fracture, or with a major surgical procedure, or significant traumatic injury within 28 days before administration of the IMP or plans a surgical procedure during the clinical trial.<br>- History or any concomitant active malignancy.<br>- A known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C.<br>- Any recent infection requiring a course of systemic anti-infective that was completed within 28 days before randomization or a serious infection (associated with hospitalization and/or which required |

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| | intravenous antibiotics) within 6 months before administration of the IMP.<br>- Inherited bleeding diathesis or coagulopathy with the risk of bleeding.<br>- Haemoptysis, thrombotic or haemorrhagic event within 6 months prior to the administration of IMP.<br>- Cerebral vascular accident, transient ischemic attack, or subarachnoid haemorrhage within 6 months prior to administration of the IMP.<br>- History and/or sign/symptoms of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to administration of the IMP.<br>- Abnormal blood pressure (normal range; systolic BP 90 ~ 139 mmHg and diastolic BP 60 ~ 89 mmHg)<br>3. Subject has an illness within 28 days prior to randomization that is classed as clinically significant by the Investigator.<br>4. Subject used prescription or non-prescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the dose of the IMP and/or subject used live or live attenuated vaccinations within 30 days prior to the dose of the IMP. Herbal supplements must be discontinued 28 days prior to the administration of the IMP.<br>5. Subject has undergone treatment with an investigational drug or participated in another clinical trial within 3 months or 5 half-lives (whichever is longer) prior to the administration of the IMP.<br>6. Subject has the previous treatment with an anti-VEGF antibody, or any other antibody or protein targeting the VEGF receptor.<br>7. Subjects who have previously been exposed to a biologic agent within 3 months prior to the administration of the IMP.<br>8. A male subject plans to father a child or donates sperms within a 6 month period following study drug administration.<br>9. Subject shows reasonable evidence of drug abuse including alcohol prior to the administration of the IMP (positive result for drug urine test and/or the opinion of the Investigator). Subject consumes more than 10 cigarettes or equivalent per day within 3 weeks prior to the administration of the IMP and/or is unable to refrain from smoking during in-house stays.<br>10. Subject donated whole blood or lost 400 mL or more blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the administration of the IMP.<br>11. Subject is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other institutionalized persons by law enforcement).<br>12. Subject shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements in the opinion of the Investigator.<br>13. Subject is not likely to complete the study for whatever reason in the opinion of the Investigator. |
| **Study Procedures:** | **Screening (Day -21 to Day -2):**<br>Subjects will sign the informed consent and undergo procedures to determine eligibility.<br>Adverse events (AEs) and concomitant medications will be monitored from the date when the informed consent form (ICF) is signed throughout the study.<br><br>**Admission (Day -1):**<br>Eligible subjects will be admitted to the clinical unit on Day -1 to undergo baseline assessments: re-check of inclusion and exclusion criteria, medical and medication history, concomitant medications, clinical laboratory, vital signs, body weight, |

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| | physical examination, and check for illicit drugs, history of drug abuse, nicotine and alcohol.<br>In case of all pertaining tests have been concluded to confirm the eligibility during screening period, randomization will be done on Day -1.<br><br>**Study Period (Day 1 [Week 1] to Day 98 [Week 14]):**<br>CT-P16, EU-approved Avastin, or US-licensed Avastin will be administered to subjects on Day 1. Subjects will be confined to the clinical unit until completion of the 24-hour assessments after IMP administration. The consecutive study visits will be carried out on an out-patient basis. Acceptable tolerance windows for each assessments are described in Section 7.1.<br>• PK analysis will be collected at pre-dose, at the end of infusion (EOI), 1 hour after the EOI, and at 4, 8, 12, and 24 hours (Day 2) after start of infusion (SOI), and on Days 3, 4, 8, 15, 29, 43, 57, 71, and 85.<br>• Clinical laboratory testing will be performed on Day 3, 8, 15, 43, and 71.<br>• Vital signs will be measured before dosing on Day 1, and on Day 3, 4, 8, 15, 29, 43, 57, 71 and 85.<br>• A 12-lead ECG will be performed on Day 3, 8, 15, 43, and 71.<br>• Physical examinations will be performed on Day 3.<br>• Hypersensitivity monitoring (vital signs measurement and 12-lead ECG) will be done on Day 1.<br>• Immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin will be assessed at pre-dose on Day 1, Day 15, 43 and Day 71.<br><br>**End-of-Study Visit (Day 99 [Week 15]):**<br>The end-of-study visit will be performed on Day 99 (Week 15).<br>Subjects will return to the research unit and undergo the following PK and safety assessments: PK sampling and immunogenicity for CT-P16, EU-approved Avastin and US-licensed Avastin, collection of information related to AEs and concomitant medications, body weight, vital signs, 12-lead ECG, clinical laboratory tests and physical examination.<br>The total duration of the participation will be up to 15 weeks for each individual subject who completes the entire clinical trial. |
| **Criteria for Evaluation:** | **Primary Endpoints**<br>*Pharmacokinetics*<br>• Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)<br>• Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)<br>• Maximum serum concentration ($C_{max}$)<br><br>**Secondary Endpoints**<br>*Pharmacokinetics*<br>• Time to $C_{max}$ ($T_{max}$)<br>• Volume of distribution during the terminal phase ($V_z$)<br>• Terminal elimination rate constant ($\lambda_z$)<br>• Terminal half-life ($t_{1/2}$)<br>• Total body clearance (CL)<br>• Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)<br>*Safety and Immunogenicity*<br>• Vital signs (blood pressure [BP], heart rate [HR], body temperature [BT], and respiratory rate [RR])<br>• Physical examination |

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| | • Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis<br>• Twelve-lead electrocardiogram (ECG)<br>• AEs and concomitant medication<br>• Adverse event of Special interest (AESI) (e.g., hypersensitivity/infusion-related reaction)<br>• Immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin |
| **Sample size assumption:** | A sample size of 42 completing subjects from each arm of the clinical study will provide 90% power to show similarity in PKs among the test product, EU-approved Avastin and US-licensed Avastin using 90% confidence interval (CI) approach based on 80%-125% equivalence margin. A coefficient of variation (CV) of 30% is assumed based upon historical PK data. The sample size is calculated from two one-sided tests with each 5% significance level using geometric mean ratio. A 10% dropout rate is anticipated so approximately 141 subjects (47 in each arm) will be enrolled. By assuming that EU-approved Avastin and US-licensed Avastin are identical, the multiplicity problem is not considered in the calculation of the sample size. |
| **Statistical Methods:** | **Pharmacokinetic analyses**<br>The statistical analysis of the log-transformed primary endpoints ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and $C_{max}$) will be based on an analysis of covariance (ANCOVA) model. The difference in least squares means between the CT-P16 and EU-approved Avastin, CT-P16 and US-licensed Avastin, EU-approved Avastin and US-licensed Avastin, and the associated 90% CIs will be determined. Back transformation will provide the ratio of geometric means and 90% CIs for these ratios.<br>Similarity of systemic exposure ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and $C_{max}$) will be determined if 90% CI for the ratio of geometric means is within the acceptance interval of 80% to 125% for the following comparisons:<br><br>• CT-P16 vs EU-approved Avastin<br>• CT-P16 vs US-licensed Avastin<br>• EU-approved Avastin vs US-licensed Avastin<br><br>For secondary endpoints, following PK parameters will be assessed:<br>Time to $C_{max}$ ($T_{max}$), volume of distribution during the terminal phase ($V_z$), terminal elimination rate constant ($\lambda_z$), terminal half-life ($t_{1/2}$), total body clearance (CL) and percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$). Pharmacokinetic parameters will be presented in listings and summarized in tables. The tables will display the following descriptive statistics: n, mean, median, standard deviation (SD), minimum, maximum, the geometric mean and CV.<br><br>**Safety and immunogenicity analyses**<br>All safety and immunogenicity analyses will be conducted on the safety population, and listed and summarized by treatment group. All reported terms for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Terminology and severity grading of AEs will be recorded based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. All safety data will be analyzed descriptively. |

# TABLE OF CONTENTS

## List of Tables

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| $AUC_{0\text{-inf}}$ | Area under the concentration-time curve from time zero to infinity |
| $AUC_{0\text{-last}}$ | Area under the concentration-time curve from time zero to the last quantifiable concentration |
| BMI | Body mass index |
| BP | Blood pressure |
| BT | Body temperature |
| bpm | Beats per minute |
| CDMP | Clinical Data Management Plan |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CK-MB | Creatine kinase–myocardial band isoenzyme |
| CL | Total body clearance |
| CNS | Central nervous system |
| CPK | Creatine phosphokinase |
| CRO | Clinical research organization |
| CRP | C-reactive protein |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of variation |
| $C_{max}$ | Maximum serum concentration |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic Data Capture |
| EOI | End of infusion |
| EOS | End of study |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |

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| GI | Gastrointestinal |
| HBsAg | Hepatitis B surface antigen |
| HIV | Human immunodeficiency virus |
| HR | Heart rate |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonization |
| IMP | Investigational medicinal product |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IRR | Infusion-related reaction |
| IV | Intravenous |
| $\lambda_z$ | Terminal elimination rate constant |
| LDH | Lactate dehydrogenase |
| mBC | Metastatic breast cancer |
| mCRC | Metastatic colorectal cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | Millimeter mercury |
| MRI | Magnetic resonance imaging |
| NSCLC | Non-small cell lung cancer |
| OTC | Over-the-counter |
| ONJ | Osteonecrosis of the jaw |
| PK | Pharmacokinetic(s) |
| PRES | Posterior Reversible Encephalopathy Syndrome |
| PT | Prothrombin time |
| RBC | Red blood cell |
| RR | Respiratory rate |
| SAE | Serious adverse event |
| SAP | Statistical analysis Plan |
| SD | Standard deviation |
| SmPC | Summary of product characteristics |
| SOI | Start of infusion |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reactions |
| $t_{1/2}$ | Terminal half-life |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to $C_{max}$ |

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| ULN | Upper limit of normal (laboratory range) |
| US | United States |
| USPI | United States Prescribing Information |
| VEGF | Vascular endothelial growth factor |
| $V_z$ | Volume of distribution during the terminal phase |
| WBC | White blood cell |
| WHO | World Health Organization |

# 1. INTRODUCTION

## 1.1 Background

Vascular endothelial growth factor (VEGF), a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiologic and pathologic angiogenesis (Ferrara et al. 2003). It is a highly conserved, homodimeric, heparin-binding glycoprotein that exists in several isoforms (Ferrara et al. 1997). VEGF mediates its effects by interacting with the membrane-bound tyrosine kinase receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR, flk-1), activating specific downstream survival and proliferation pathways. VEGF is considered essential for normal developmental vasculogenesis, and there is substantial evidence implicating VEGF as a critical factor in tumor angiogenesis (Ferrara et al. 2003). Transfection of Chinese hamster ovary cells with expression vectors encoding VEGF allows these cells to form tumors in nude mice (Ferrara et al. 1993). Increased VEGF expression has been described in most human tumors and in many instances is correlated with an adverse prognosis (increased risk of tumor recurrence and metastasis and decreased survival) (Takahashi et al. 1995; Takahashi et al. 1997; Warren et al. 1995).

Bevacizumab is a humanized monoclonal antibody directed against VEGF. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. By blocking the endothelial interaction of VEGF and its receptors, bevacizumab serves as an antiangiogenic agent.

The reference product, Avastin, is formulated as a 25 mg/mL concentrate for solution for infusion, presented in single-use, type 1 glass vials containing 100 mg or 400 mg of bevacizumab. The Avastin drug product is a clear to slightly opalescent, colourless to pale brown liquid containing the excipients, α, α-trehalose dihydrate (60 mg/ml), sodium phosphate (51 mM, pH 6.2), polysorbate 20 (0.04%), and water for injections. The product is to be diluted in 0.9% sodium chloride solution prior to administration.

CT-P16, containing the active ingredient bevacizumab, is being developed as a similar biological medicinal product to Avastin, which currently has received approval in both European Union (EU) and United States (US) for the indications shown in the Avastin Summary of Product Characteristics (SmPC, 2017) and Avastin United States Prescribing Information (USPI, 2016).

CT-P16 drug product will have the same pharmaceutical form and strength as the EU-approved/US-licensed Avastin, and is intended to be highly analytically comparable to EU-approved/US-licensed Avastin. As for EU-approved/US-licensed Avastin, the bevacizumab

active ingredient of CT-P16 is produced by recombinant DNA technology in a CHO cell expression system and purified by a suitable process.

Avastin has been approved in a variety of tumor types, including metastatic carcinoma of the colon or rectum; metastatic breast cancer (mBC) (EU only); unresectable, advanced, metastatic, or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous histology; advanced and/or metastatic renal cell cancer; epithelial ovarian, fallopian tube or primary peritoneal cancer; persistent, recurrent, or metastatic carcinoma of the cervix; and glioblastoma (US only).

As CT-P16 is being developed under a global development plan, the pharmacokinetic (PK) profile of CT-P16 and two reference products from different sources (EU-approved Avastin and US-licensed Avastin) will be compared to demonstrate PK equivalence in this Phase 1 study.

## 1.2 Rationale for the Clinical Study

The introduction of biosimilar (follow-on) medicinal products is desirable as they will enhance patient access by expanding the field of competing biotechnological treatments. The purpose of this clinical study is to compare the PK, safety, tolerability and immunogenicity of the proposed biosimilar test product CT-P16 with EU-approved Avastin and US-licensed Avastin after a single intravenous (IV) infusion of 5 mg/kg of each product to healthy adult subjects following the recommendations of the Food and Drug Administration (FDA) guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA 2015)" and EMA guidance "Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010) (CHMP 2012).

With regards to the selection of dose, doses of Avastin between 5 and 15 mg/kg are used in clinical practice. From a safety perspective, it is considered best to administer the lowest recommended therapeutic dose in studies of healthy subjects. Also, the 5 mg/kg dose is proposed in this Phase 1 PK study, since bevacizumab PK is linear at doses between 1 and 10 mg/kg and use of 5 mg/kg is further supported in terms of assessment of immunogenicity as higher doses are theoretically expected to be less immunogenic. According to clinicaltrials.gov, 5 mg/kg has been administered to healthy male volunteers in another study of a biosimilar bevacizumab (Pfizer's PF-06439535) and has been shown to be well tolerated, with no signs of unexpected side effects or cardiotoxicity (Knight et al. 2016).

Healthy subjects have been selected for this study in order to avoid potentially high variability of the exposure of bevacizumab if administered to patients with metastatic colorectal cancer or non-squamous non-small cell lung cancer, which would introduce a bias into the attainment of

the primary study objective. A parallel-group design will be used in this study to prevent potential crossover effects.

## 1.3 Risk-Benefit Assessment

Information about the risk following the administration of bevacizumab was taken from the Avastin SmPC (2017) and Avastin USPI (2016) of EU-approved and US-licensed Avastin.

***Gastrointestinal (GI) perforations and Fistulae:*** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with Avastin and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

***Non-GI Fistulae:*** Patients may be at increased risk for the development of fistulae when treated with Avastin. Avastin should be permanently discontinued in patients with tracheoesophageal fistula or any Grade 4 fistula [US National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE) Version 3)]. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Avastin should be considered.

***Wound healing complications***: Avastin may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with Avastin. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

***Hypertension:*** An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure (BP) is generally recommended during therapy. In most cases hypertension was controlled adequately using

standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avastin should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

***Posterior Reversible Encephalopathy Syndrome (PRES):*** There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.

***Proteinuria:*** Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that all Grade (CTCAE Version 3) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome) (CTCAE Version 3).

***Arterial thromboembolism:*** In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents, transient ischaemic attacks and myocardial infarctions was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Patients receiving Avastin plus chemotherapy, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with Avastin. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions.

***Venous thromboembolism:*** Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under Avastin treatment. Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events. Avastin should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (CTCAE Version 3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (CTCAE Version 3).

***Haemorrhage:*** Patients treated with Avastin have an increased risk of haemorrhage, especially tumor-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (CTCAE Version 3). Patients with untreated central nervous system (CNS) metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomized clinical trials. Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases of intracranial bleeding. There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly (CTCAE Version 3).

***Pulmonary haemorrhage/haemoptysis:*** Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage /haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (> 2.5 mL of red blood) should not be treated with Avastin.

***Congestive heart failure (CHF):*** Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin. Most of the patients who experienced CHF had mBC and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present. CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of mBC who did not receive concurrent anthracycline treatment (CTCAE Version 3).

***Neutropenia and infections:*** Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

***Hypersensitivity reactions/infusion reactions:*** Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

***Osteonecrosis of the jaw (ONJ):*** Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and intravenous bisphosphonates are administered simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

***Ovarian failure/fertility:*** Avastin may impair female fertility. Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin.

***Embryo-fetal Toxicity:*** Avastin may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin.

This study will therefore include close monitoring of safety and toxicity reactions. Subjects who received monoclonal antibody or biologic agent within 3 months prior to the administration of the Investigational medicinal product (IMP) (in a clinical trial or as treatment) will be excluded from study participation as they may have developed antibodies against bevacizumab, which might be a trigger adverse reaction. Antibodies against bevacizumab may also interfere with the primary study objective as the exposure to the IMP may be precluded due to antibody binding and therefore may distort the PK endpoints. Further, the potential immunogenicity of CT-P16, EU-approved and US-licensed Avastin will be evaluated.

The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect all expected treatment-emergent adverse events (TEAEs). As

bevacizumab is infused only once over 90 minutes (± 5 min) in treatment-relevant dose, the overall risk of the study for healthy subjects is considered to be acceptable.

# 2. STUDY OBJECTIVES

## 2.1 Primary Objective

- To demonstrate the similarity of the PK in terms of area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$), and maximum serum concentration ($C_{max}$) of CT-P16, US-licensed Avastin and EU-approved Avastin in healthy male subjects (CT-P16 to EU-approved Avastin, CT-P16 to US-licensed Avastin, and EU-approved Avastin to US-licensed Avastin).

## 2.2 Secondary Objective(s)

- To assess the additional PK parameters of CT-P16, US-licensed Avastin, and EU-approved Avastin in healthy male subjects.
- To evaluate the safety and immunogenicity of CT-P16, US-licensed Avastin, and EU-approved Avastin in healthy male subjects.

# 3. OVERALL DESIGN AND PLAN OF THE STUDY

## 3.1 Overview

This study is a double-blind, three-arm, parallel group, single-dose study. A total of 141 healthy male subjects aged between 19 and 55 years will be enrolled; 47 subjects in each of the 3 arms of the clinical study. In each arm, all subjects will receive a single dose of CT-P16, EU-approved Avastin, or US-licensed Avastin by IV infusion for 90 min (±5 min) on Day 1 followed by 15 weeks during which the PK, safety and immunogenicity measurements will be made.

Subjects will be screened for eligibility within 21 to 2 days before the infusion of the IMP after they have signed an informed consent. Multiple visits may be needed during the screening period to complete study-related assessments.

Eligible subjects will be admitted to the clinical unit on Day –1 to undergo baseline assessments and will be randomized on Day –1 to receive one of CT-P16, EU-approved Avastin, or US-licensed Avastin once all eligibility criteria have been confirmed. Subjects will be confined to the clinical unit until completion of the 24-hour assessments after IMP administration. The consecutive study visits will be carried out on an out-patient basis. Blood for PK analysis will be collected up to Day 99. Safety will be assessed throughout the study by collection of information about AEs and concomitant medication, by clinical laboratory testing, measurement of vital signs, recording of 12-lead ECGs, physical examination and assessment of the immunogenicity of CT-P16, EU-approved Avastin, and US-licensed Avastin. An end-of-study (EOS) examination will take place on Day 99.

The total duration of the participation will be up to 15 weeks for each individual subject who completes the entire clinical trial.

Please refer to Section 7.2, Table 2, Table 3, and Table 4 for a detailed list of procedures performed on each study day/visit.

## 3.2 Endpoints

### 3.2.1 Primary endpoints

**Pharmacokinetics**

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)
- Maximum serum concentration ($C_{max}$)

### 3.2.2 Secondary endpoints

**Pharmacokinetics**

- Time to $C_{max}$ ($T_{max}$)
- Volume of distribution during the terminal phase ($V_z$)
- Terminal elimination rate constant ($\lambda_z$)
- Terminal half-life ($t_{1/2}$)
- Total body clearance (CL)
- Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)

**Safety and Immunogenicity**

- Vital signs (blood pressure [BP], heart rate [HR], body temperature [BT], and respiratory rate [RR])
- Physical examination
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Twelve-lead electrocardiogram (ECG)
- Adverse events (AEs) and concomitant medication
- Adverse event of special interest (AESI) (e.g., hypersensitivity/infusion-related reaction [IRR])
- Immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin

## 3.3 Justification of the Study Design

The purpose of this clinical trial is to compare the PK, safety and immunogenicity of the proposed biosimilar test product CT-P16 with EU-approved Avastin and US-licensed Avastin after a single IV infusion of 5 mg/kg of each product to healthy male subjects. The clinical trial will be conducted according to the recommendations of the FDA guidance "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (US FDA guidance 2015)" and EMA guidance "Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010) (CHMP 2012).

# 4. STUDY POPULATION

The study population will consist of healthy male subjects. Subjects must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria, according to the criteria outlined below (Sections 4.2 and 4.3).

## 4.1 Number of Subjects

A total of 141 subjects will be enrolled in the clinical study, and 47 subjects will be randomized into each of 3 study arms (CT-P16, EU-approved Avastin or US-licensed Avastin).

## 4.2 Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Subject is able to understand and to comply with protocol requirements, instructions, and restrictions.
2. Subject voluntarily agrees to participate in this study and has given a written informed consent prior to performing any of the screening procedures.
3. Healthy male subjects between the ages of 19 and 55 years, both inclusive (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including BP and HR measurement, 12-lead ECG and clinical laboratory tests prior to the administration of IMP).
4. Body Mass Index (BMI) between 18.0 and 29.9 $kg/m^2$ (both inclusive) and a body weight ≥50 kg.
5. Male subject, unless surgically sterile for at least 6 months before the time of the administration of IMP, must be willing to abstain from sexual intercourse or willing to use a condom in addition to having his female partner of childbearing potential use an additional form of contraception such as an intra-uterine device, barrier method with spermicide, oral contraceptive, injectable progesterone, sub-dermal implant from Day 1 until at least 6 months after the administration of the IMP. The female partner of the participating subject should be familiar with the use of the respective contraceptive methods. Intra-uterine devices and hormonal methods for contraceptive should have been used for at least one menstruation cycle before infusion.

## 4.3 Exclusion Criteria

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Subject is a female.
2. Subject has a medical history and/or current presence of disease including one or more of the following(s):
   - Clinically significant allergic reactions (spontaneous, atopic allergy, or following drug administration) such as asthma, urticaria, angio-oedema, and eczematous dermatitis, hypersensitivity, also including known or suspected clinically relevant drug hypersensitivity to benzyl alcohol or any components of the test and reference IMP formulation or other similar drugs.
   - Cardiac, gastrointestinal, renal, hepatic, hematological (including pancytopenia, aplastic anaemia or blood dyscrasia), metabolic (including known diabetes mellitus), neurologic or pulmonary diseases classed as significant by the Investigator.
   - Non-healing wound, ulcer, bone fracture, or with a major surgical procedure, or significant traumatic injury within 28 days before administration of the IMP or plans a surgical procedure during the clinical trial.
   - History or any concomitant active malignancy.
   - History of and/or current immunodeficiency including infection with hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or positive result to the screening test for those infections.
   - Any recent infection requiring a course of systemic anti-infective that was completed within 28 days before randomization or a serious infection (associated with hospitalization and/or which required intravenous antibiotics) within 6 months before administration of the IMP.
   - Inherited bleeding diathesis or coagulopathy with the risk of bleeding.
   - Haemoptysis, thrombotic or haemorrhagic event within 6 months prior to the administration of IMP.
   - Cerebral vascular accident, transient ischemic attack, or subarachnoid haemorrhage within 6 months prior to administration of the IMP.
   - History and/or sign/symptoms of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to administration of the IMP.
   - Abnormal blood pressure (normal range; systolic BP 90 ~ 139 mmHg and diastolic BP 60 ~ 89 mmHg).
3. Subject has an illness within 28 days prior to randomization that is classed as clinically significant by the Investigator.

4. Subject used prescription or non-prescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the administration of the IMP and/or subject used live or live attenuated vaccinations within 30 days prior to the dose of the IMP. Herbal supplements must be discontinued 28 days prior to the administration of the IMP.
5. Subject has undergone treatment with an investigational drug or participated in another clinical trial within 3 months or 5 half-lives (whichever is longer) prior to the administration of the IMP.
6. Subject has the previous treatment with an anti-VEGF antibody, or any other antibody or protein targeting the VEGF receptor.
7. Subjects who have previously been exposed to a biologic agent within 3 months prior to the administration of the IMP.
8. A male subject plans to father a child or donates sperms within a 6-month period following study drug administration.
9. Subject shows reasonable evidence of drug abuse including alcohol prior to the administration of the IMP (positive result for drug urine test and/or the opinion of the Investigator). Subject consumes more than 10 cigarettes or equivalent per day within 3 weeks prior to the administration of the IMP and/or is unable to refrain from smoking during in-house stays.
10. Subject donated whole blood or lost 400 mL or more blood within 8 weeks (plasma/platelets donation within 4 weeks) prior to the administration of the IMP.
11. Subject is vulnerable (e.g., employees of the clinical trial site or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison or other institutionalized persons by law enforcement).
12. Subject shows evidence of a condition (psychological, emotional problems, any disorders or resultant therapy) that is likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements in the opinion of the Investigator.
13. Subject is not likely to complete the study for whatever reason in the opinion of the Investigator.

## 4.4 Subject Withdrawal and Replacement

Subjects will be withdrawn from the study prematurely for the following reasons:

- Withdrawal of consent: Subjects have the right to withdraw from the study at any time for any reason. If the withdrawal occurs following IMP dosing, the subject will be asked to attend the clinical unit for safety assessments at the EOS examination.

- Protocol violation of concern: The subject will be withdrawn by the Investigator after discussion with the Sponsor:
  - If protocol violations or intercurrent illnesses that may affect study objectives occur, or
  - If it is discovered that the subject has entered the study in violation of the protocol.
- Adverse event: If a subject reports symptoms that are considered unacceptable by the Investigator and/or Sponsor, he will be withdrawn from the study, e.g. abnormal laboratory values such as alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevated >5 times of upper limit of normal (ULN) laboratory range or uric acid >10 mg/dL or > 0.59 mmol/L with physiological consequences (according to Grade 4, CTCAE Version 4.03).

The appropriate AE page in electronic case report form (eCRF) is to be completed. If premature withdrawal occurs for any reason, the Investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the eCRF.

Subjects who discontinue the study will be asked to participate in the safety assessments of the EOS procedures including a physical examination, vital sign measurements, 12-lead ECG and standard safety laboratory tests, if possible. All subjects who withdraw from the study because of an AE or clinical laboratory abnormality will be followed-up at suitable intervals in order to evaluate the course of the AE or laboratory abnormality and to ensure resolution or stabilization of the event. The subsequent outcomes of these events will be recorded in the eCRF.

Subjects will be allowed to rescreen only once, however, subjects withdrawn (after randomization) will not be replaced.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show due diligence by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc.

## 4.5 Premature Termination of the Clinical Trial

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study may be terminated at the Sponsor’s discretion also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study (including but not limited to AEs, laboratory and/or vital sign

abnormalities that in the opinion of the Investigator/Sponsor are unacceptable for a further conduct of the study);

- Failure to enroll subjects at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the IMP.

Should the study be terminated and/or the site closed for whatever reason, Study related documents should be archived at the site according to the section 9.6. Used/unused IMP should be managed according to section 5.4. Any actions of the Investigator required for assessing or maintaining study subject safety will continue as required, despite termination of the study by the Sponsor.

If the study is terminated for whatever reason, all subjects will be kept fully informed.

# 5. INVESTIGATIONAL MEDICINAL PRODUCT

## 5.1 Identity of the Investigational Medicinal Products

The IMPs that will be used in this study are outlined in Table 1.

**Table 1. Identity of Investigational Products**

| IMP Name | Dosage form | Strength | Route |
|---|---|---|---|
| CT-P16 | Liquid for concentrate for solution for infusion | 400 mg | IV |
| EU-approved Avastin | Liquid for concentrate for solution for infusion | 400 mg | IV |
| US-licensed Avastin | Liquid for concentrate for solution for infusion | 400 mg | IV |

IMP = investigational medicinal product; IV = intravenous.

## 5.2 Dose Rationale Including Time of Dosing

The IMP (CT-P16, EU-approved Avastin, or US-licensed Avastin) will be dosed once as an IV infusion over 90 min (±5 min). The lowest approved dose for Avastin indications is 5 mg/kg body weight which is the typical dose used for treatment of metastatic colorectal cancer (mCRC) as lined out in the prescribing information of Avastin.

## 5.3 Supply, Packaging, Labeling and Storage

The test IMP (CT-P16, EU-approved Avastin and US-licensed Avastin) will be supplied by CELLTRION, Inc. The IMPs will be packaged and labeled according to applicable local and regulatory requirements.

A label will be attached to the outside of each subject kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Subject number/site number
- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator’s name
- Storage instructions
- Caution statement (for clinical trial use only)
- CELLTRION’s contact name and address
- Expiry date

All IMP supplies must be stored in accordance with the manufacturer's instructions and will be stored in a refrigerator at 2°C to 8°C and the vials will be protected from light. Until dispensed to the subjects, the IMPs will be stored in a securely locked area, accessible to authorized personnel only.

## 5.4 Drug Accountability, Dispensing and Destruction

It is the responsibility of the clinical Investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The drug accountability will be verified by the monitor during on-site monitoring visits.

The Investigator agrees not to supply the study drug to any person other than sub-Investigator, designated staff, and the subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects unless approved by CELLTRION, Inc.

During the study, study drugs may need to be returned to the depot of origin. Unused study drug vials should be returned to the depot of origin. Accountability of the product must be completed at the site level and discrepancies, if any, need to be resolved prior to return. Only if it is written in standard operating procedures (SOPs) or documentation in place, the used vials can be destroyed locally. The list of destroyed vials must be recorded. The Investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with CELLTRION, Inc.

Details in study drugs accountability and destruction will be followed according to the pharmacy manual.

## 5.5 Method of Assigning Subjects to Treatment Group

### 5.5.1 Screening numbers

All screened subjects are assigned unique screening or run-in numbers. These numbers will be used to identify subjects during study period.

### 5.5.2 Randomization

Randomization will occur at Day -1 after all baseline assessments have been performed and eligibility for the study has been confirmed. Subjects will be randomly assigned to treatment groups (1:1:1 ratio to CT-P16, EU-approved Avastin, or US-licensed Avastin) using the Interactive Web Response System (IWRS). The randomization will be balanced by using permuted blocks and will be stratified by body weight (<70 kg vs ≥70 kg) and site.

## 5.6 Administration of Investigational Medicinal Products

On Day 1, a subject will receive an IV infusion of CT-P16, EU-approved Avastin, or US-licensed Avastin over 90 minutes (± 5 min) with an infusion pump. The infusion will take place starting in the morning under consideration of dietary and fluid restrictions (see Section 7.3.1).

Subject will be residing in a semi-recumbent position while they receive the infusion of the IMP. By exception, the subject may get up (e.g., toilet visit) but he has to be instructed to call the study staff for assistance. Appropriate medical measures must be directly available in case of IRRs. The infusion must be interrupted if the intensity of the IRRs does not justify the continuation of the administration and would impose the subject to an unbearable risk as deemed by the Investigator or if a situation arises where the stopping rules apply (see Sections 4.4 and 4.5).

The infusion of CT-P16, EU-approved Avastin or US-licensed Avastin can be stopped immediately in the case of safety issues occurring during the infusion period at the Investigator's discretion. An interruption of the infusion is permitted if the Investigator deems this appropriate (e.g., in case of signs dyspnea or clinically significant hypertension). The infusion will be resumed as soon as the cause of the interruption is resolved. If feasible, subjects will be followed for the safety and PK assessments given by the study design after they have received the infusion.

## 5.7 Compliance

The infusion will be performed by trained, qualified personnel designated by the Investigator. The date and time of start of infusion (SOI) and end of infusion (EOI) will be documented. Comments will be recorded if there are any deviations from the planned dosing procedures.

## 5.8 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. All IMPs will be diluted by a designated unblinded pharmacist, and will be supplied to the treating physician or designee in a blinded manner, in identical infusion bags, thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency (where knowledge of the IMP administered would affect the treatment of the emergency) or regulatory requirement (e.g., for serious adverse events [SAEs] or death).

The decision to break the blind will be made on a case-by-case basis, at the discretion of the Investigator/Sponsor. If the blind is broken, the date, time and reason must be recorded in the eCRF, and any associated AE report.

If an emergency unblinding becomes necessary, the Investigator should notify the Sponsor/Medical Monitor prior to unblinding, if possible, unless identification of the IMP is required for emergency therapeutic measures. If the Investigator is unable to contact the Sponsor/Medical Monitor, the Investigator may, in an emergency, determine the identity of the treatment by using the applicable procedure in the IWRS.

If a subject is unblinded, the subject must be withdrawn from the clinical study and procedures accompanying withdrawal are to be performed.

Suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the Competent Authorities.

The overall randomization code will be broken only for reporting purposes once all final clinical data have been entered into the database and all data queries have been resolved, and the assignment of subjects to the analysis sets has been completed. The randomization code will not be revealed to study subjects, parents or guardians, study site staff, or Investigators.

## 5.9 Concomitant Medications

Any medicinal product, prescribed or over-the-counter (OTC) drug, including herbal and other non-traditional remedies, is considered a concomitant medication. Prior and concomitant medication use will be recorded for the 30 days prior to the screening visit until the EOS visit. Concomitant medication use is permitted if indicated by the Investigator for premedication or treatment of an AE.

Subjects who had an exposure to a monoclonal antibody or currently used a biologic (including but not limited to anti-VEGF antibody) within 3 months prior to the administration of the IMP must be excluded. The use of OTC medications (including vitamins), or prescription medications within 7 days or 5 half-lives (whichever is longer) prior to the dose of the IMP until EOS will not be permitted. For live or attenuated vaccines, the vaccination within 30 days prior to the dose of the IMP until EOS will not be permitted. Herbal supplements must be discontinued 28 days prior to the administration of the IMP until EOS. Refer to Section 4.3 for exclusion criteria on concomitant medications and timing.

## 5.10 Treatment of Overdose

An overdose is defined as 10% or more than the dose prescribed. Overdose may be symptomatic or asymptomatic. Sign and Symptoms associated with an overdose must be recorded as an AE and recorded as detailed in Section 6.2.2.2, and an overdose without signs or symptoms must be documented in the IMP section in the eCRF.

Although not strictly due to an overdose, IRR are possible and hypersensitivity must be monitored according to the details in Section 6.2.3.

# 6. VARIABLES AND METHODS OF ASSESSMENT

## 6.1 Pharmacokinetic Variables

The following PK parameters will be determined for CT-P16, EU-approved Avastin and US-licensed Avastin in serum following single dose administration:

**Primary Endpoints**

- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$)
- Maximum serum concentration ($C_{max}$)

**Secondary Endpoints**

- Time to $C_{max}$ ($T_{max}$)
- Volume of distribution during the terminal phase ($V_z$)
- Terminal elimination rate constant ($\lambda_z$)
- Terminal half-life ($t_{1/2}$)
- Total body clearance (CL)
- Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation ($\%AUC_{ext}$)

Blood will be processed and serum analyzed by a validated method for concentrations of CT-P16, EU-approved Avastin and US-licensed Avastin. The PK parameters listed above will be calculated from the serum concentration-actual time profiles. The non-compartmental analysis will be performed using [redacted].

## 6.2 Safety Variables

### 6.2.1 Medical History, Demographic and Other Baseline Information

The medical history comprises the following:

- General medical history
- Medication history

The following demographic information will be recorded:

- Age
- Gender
- Race

- Height [cm], without shoes
- Body weight [kg], without shoes
- Body Mass Index [kg/m²]

Other baseline characteristics will be recorded as follows:

- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- Special diet (vegetarian)
- History of blood or plasma/platelets donation or loss

### 6.2.2 Adverse Events

All AEs will be collected from the date the informed consent form (ICF) is signed and AE reporting will continue until the end of the subject's participation in the study.

#### 6.2.2.1 Definitions

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

All AEs, including intercurrent illnesses, occurring during the clinical study will be documented in the eCRF. Concomitant illnesses, which existed prior to signing the ICF, will not be considered AEs unless they worsen during the study period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

A TEAE is defined as an AE that begins or that worsens in severity after administration of the IMP. If laboratory test abnormalities occur after IMP infusion, only the clinically significant cases should be considered TEAEs. The clinically significant cases are ones that:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)

- Require dose modification or dose delay
- Are associated with clinical signs or symptoms judged by the Investigator to have a clinically significant impact

Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

#### 6.2.2.2 Recording of Adverse Events

Adverse events may be volunteered spontaneously by the study subject or discovered by the study staff during physical examinations or by asking an open, non-leading question such as "How have you been feeling since you were last asked?" All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) and status of AE outcome, severity, and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to the IMP.

All AEs should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

#### 6.2.2.3 Assessment of Adverse Events

Terminology and severity grading of AEs will be recorded based on CTCAE Version 4.03. MedDRA version 20.0 or later will be recorded in statistical analysis plan (SAP) and used for reporting purpose (i.e. clinical study report and regulatory requirement).

Each AE will be assessed by the Investigator with regard to the categories discussed in the sections below.

##### 6.2.2.3.1 Intensity

Investigator will assess all AEs for severity in accordance with the following criteria:

| | |
|---|---|
| Grade 1: | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| Grade 2: | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of daily living (ADL)*. |
| Grade 3: | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| Grade 4: | Life-threatening consequences; urgent intervention indicated. |
| Grade 5: | Death related to AE. |

Source: CTCAE Version 4.03
Note: a semicolon indicates "or" within each description.
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording the change of intensity of the respective AE, with the amended severity grade, and the date (and time, if known) of the change.

In the case of any event requiring medical intervention occurring during the in-house stay, the Investigator will institute general supportive measures including, where necessary, respiratory assistance and cardiopulmonary resuscitation.

#### 6.2.2.3.2 Causality

The Investigator will assess the causality/relationship between the IMP and the AE and record that assessment results in the eCRF.

The most likely cause of an AE will be indicated in the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to IMP will be described using following classification:

- Definite:
  - This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions do not appear to explain the event.
- Probable:
  - This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator′s clinical experience, the association of the event with the study drug seems likely.

- Possible:
  - This relationship suggests that treatment with the IMP caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the IMP, but could also have been produced by other factors.
- Unrelated:
  - This relationship suggests that there is no association between the IMP and the reported event.

#### 6.2.2.3.3 Expectedness

An unlisted or unexpected AE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g. Investigator's brochure [IB]) for an unapproved investigational product or the label (e.g. prescribing information or SmPC) for an approved product. If the IB for CT-P16 is delayed, the SmPC or prescribing information will take precedence.

#### 6.2.2.3.4 Seriousness

An SAE is defined as any untoward medical occurrence that:

- Results in death;
- Is life-threatening; this means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- Requires at least 24-hour hospitalization or prolongation of expected length of stay. Hospitalization for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not serious adverse events by these criteria;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect;
- Is another important medical event (see below).

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

#### 6.2.2.3.5 Adverse Events of Special Interest

An 'adverse event of special interest' is an AE or occurrence that is designated to be of special interest and must be reported to the Sponsor using the same reporting process as an AE.

The following events are considered events of clinical interest for this study:

- Infusion-related reaction/hypersensitivity

All AEs related to infusion include but are not limited to the following: urticaria, hypotension or hypertension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, or anaphylactoid events.

### 6.2.2.4 Reporting of Serious Adverse Events

The Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to IMP. All SAEs will be recorded from signing of informed consent until the EOS visit. Serious AEs occurring after the EOS visit and coming to the attention of the Investigator must be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the IMP.

The Investigator is responsible for data entry in the electronic data capture system within 24 hours of awareness of an SAE. In the event that is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax to clinical research organization (CRO) Pharmacovigilance team within 24 hours of awareness of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number

- Subject number
- Gender
- Age
- Name of Investigator and full study center address
- SAE term
- Criterion for classification as 'serious'
- Name of IMP and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification)

The Sponsor will request clarification of omitted or discrepant information from the initial notification. The Investigator or an authorized delegate is responsible for faxing the requested information to the Sponsor within 24 hours of the Sponsor's request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g. hospital reports, consultant reports, autopsy reports etc.), with the study subject's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and faxed to the Sponsor within 24 hours of receipt of the information. If a new SAE Report Form is received, then the Investigator must sign and date the form. The Sponsor may also request additional information on the SAE, which the Investigator or an authorized delegate must fax to the Sponsor within 24 hours of the request.

#### 6.2.2.5 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has been resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Sponsor/Medical Monitor, until there is a satisfactory explanation for the changes observed, or until the subject is lost to Follow-up.

#### 6.2.2.6 Procedure for Notification of Serious Adverse Event and Suspected Unexpected Serious Adverse Reactions to Institutional Review Boards

If required by applicable local regulations, the Investigator shall promptly notify the relevant Institutional Review Board (IRB) (in addition to the Sponsor) of any SAE (including follow-up SAEs) and SUSARs that occurred at his/her site or brought to his/her attention by the Sponsor. The Investigator shall verify that the IRB acknowledges receipt of the information.

The Sponsor will provide annual safety reports to the competent authorities and ethics committees responsible for the clinical study. These updates will include information on SUSARs and other relevant safety findings.

#### 6.2.2.7 Pregnancy

Women will be excluded from this study (see Section 4.3). However, the following directives describe the procedures and measurements that are to be considered if women of childbearing potential become pregnant who are partners of male subjects participating in this study.

- If a female partner of a male subject who has been exposed to the IMP becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. The baby will be followed for 1 year after the birth, provided consent from the pregnant partner of the subject is obtained.

- The Sponsor or its designee has a responsibility to monitor the outcome of all pregnancies reported during the clinical study.

- Each pregnancy must be reported by the Investigator to the Sponsor on the initial pregnancy report form within 24 hours after becoming aware of the pregnancy. The Investigator must follow up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has finished.

- All outcomes of pregnancy must be reported by the Investigator to the Sponsor on the pregnancy outcome report form within 24 hours after he/she has gained knowledge of the normal delivery or elective abortion.

- The site must complete the supplied pregnancy form (the partner of a male subject) and return it to CRO Pharmacovigilance team within 24 hours (see Section 6.2.2.4).

### 6.2.3 Hypersensitivity Assessment

Hypersensitivity will be assessed by routine clinical monitoring including BP, HR, RR and BT measurement and 12-lead ECG and recorded in accordance with the Schedule of Assessment for Hypersensitivity Monitoring (Table 3). Emergency equipment such as adrenaline, antihistamines, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available. Subjects who develop a life-threatening IRR must be withdrawn from study.

### 6.2.4 Clinical Laboratory Assessments

The safety laboratory analyses of blood including hematology, coagulation, and clinical chemistry, as well as urine drug screen will be performed according to validated methods and procedures. Laboratory analyses will be performed by the local laboratories.

The following laboratory variables will be determined in accordance with the Schedule of Assessments (Table 4):

- **Hematology**: The following hematology parameters were assessed: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, absolute neutrophil count (ANC), and platelets.
- **Clinical chemistry**: The following clinical chemistry parameters were assessed: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, chloride, total cholesterol, creatine phosphokinase (CPK), creatine kinase–myocardial band isoenzyme (CK-MB), creatinine, creatinine clearance (estimated by Modification of Diet in Renal Disease [MDRD]), C-reactive protein (CRP), gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), triglycerides, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, Troponin I.
- **Coagulation**: Fibrinogen, international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT).
- **Urinalysis**: Color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination.
- **Urine drug, alcohol and nicotine:** screen for drugs of abuse including the following: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and cannabinoids. The test for drugs of abuse will be performed during the Screening Period only. The history of Drug abuse, Alcohol and nicotine will be checked by medical history taking by the Investigator during the Screening Period and Day -1.

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the screening period is indicated as clinically significant, the study subject will NOT be allowed into the study without permission of the Sponsor/Medical Monitor. However, retest is permitted only once during screening period by the Investigator's judgment. Additional testing during the study period may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the EOS visit, it should be recorded as an AE and the study subject will be followed until the test(s) has (have) normalized or stabilized.

### 6.2.5 Vital Signs

Vital signs will be assessed at time points specified in the Schedule of Assessments (Table 4). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg]);
- Heart rate (beats per minute [bpm]);
- Body temperature (°C);
- Respiratory rate (breaths per minute).

Blood pressure (BP), HR, RR and BT recordings will be made after the study subject has been resting for at least 5 minutes.

### 6.2.6 Electrocardiograms

The 12-lead ECGs will be obtained after the subject has been rested for at least 5 minutes and will be performed at the time points specified in the Schedule of Assessments (Table 4).

Twelve-lead ECG for hypersensitivity monitoring will also be performed according to the Schedule of Assessment for Hypersensitivity Monitoring (Table 3).

If, following ECG review by the Investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the subject will be referred to a cardiologist and the event will be recorded in the source documents and the eCRF.

### 6.2.7 Physical Examinations

Physical examinations will be performed at time points specified in the Schedule of Assessments (Table 4).

The physical examination includes an assessment of general appearance and a review of systems. Information about the physical examination will be recorded by the Investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded as such in the source documents.

## 6.3 Immunogenicity Variables

The potential immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin will be assessed in samples collected at the time points specified in the Schedule of Assessments (Table 4).

The immunogenicity of CT-P16, EU-approved Avastin and US-licensed Avastin will be assessed at baseline and post-treatment serum measures by anti-drug antibodies in a validated immunoassay.

## 6.4 Sample Collection, Storage and Shipment

### 6.4.1 Pharmacokinetic Sampling

Blood will be collected per blood sampling time points for PK assessment sample at the time points specified in the Schedule of Assessments (Table 2). All samples will be collected as close as possible to the scheduled time point and the actual sampling time will be recorded.

The samples will be split into separate containers or tubes, and processed, stored, and shipped under the appropriate conditions as outlined in a separate laboratory manual. [redacted].

### 6.4.2 Clinical Laboratory Testing

Clinical testing will be performed locally at the time points specified in the Schedule of Assessments (Table 4).

### 6.4.3 Immunogenicity Sampling

Serum will be collected at the time points specified in the Schedule of Assessments (Table 4). The samples will be split into separate containers or tubes, and processed, stored, and shipped under the appropriate conditions as outlined in a separate laboratory manual. [redacted].

# 7. STUDY CONDUCT

## 7.1 Schedule of Assessments

The study consists of a screening visit (Day –21 to Day –2), in-house stay (Day –1 to Day 2), and further visits on an out-patient basis which will be conducted on Day 3, Day 4, Day 8, Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and Day 99. The subjects will receive the study drug on Day 1, and assessments for PK and safety will be carried out during the in-house stay and further out-patient visits.

The EOS visit for safety and PK assessments will take place on Day 99. The approximate study duration for an individual subject will be 15 weeks.

Study procedures can be performed within the allowed flexibility range without protocol violation. Details of blood sampling time points and acceptable tolerance windows for PK assessments are described in Table 2.

**Table 2. Blood sampling time points for PK assessment**

| Day of study period | Time point | Window |
|---|---|---|
| Day 1 | Pre-dose | Before study drug infusion |
| | **End of infusion** | Immediately end of infusion (within +5 minutes after **EOI**) |
| | **1 hour after EOI** | ± 15 minutes |
| | 4 hours after SOI | |
| | 8 hours after SOI | |
| | 12 hours after SOI | |
| Day 2 | 24 hours after SOI | ± 15 minutes |
| Day 3 | 48 hours after SOI | ± 1 hour |
| Day 4 | 72 hours after SOI | |
| Day 8 | 168 hours after SOI | ± 4 hours |
| Day 15 | 336 hours after SOI | |
| Day 29 | 672 hours after SOI | ± 1 day |
| Day 43 | 1,008 hours after SOI | |
| Day 57 | 1,344 hours after SOI | |
| Day 71 | 1,680 hours after SOI | ± 3 days |
| Day 85 | 2,016 hours after SOI | |
| Day 99 | 2,352 hours after SOI | |

**Abbreviation: EOI = End of infusion, SOI = Start of infusion**

For hypersensitivity monitoring, vital signs and 12-lead ECG will be done. Assessment time points and acceptable tolerance windows for hypersensitivity monitoring are described in Table 3.

**Table 3. Schedule of Assessment for Hypersensitivity Monitoring**

| Assessment | Day of study period | Time points | Window |
|---|---|---|---|
| Vital sign | Day 1 | 15 minutes after SOI | ± 5 minutes |
| | | 30 minutes after SOI | |
| | | 1 hour after SOI | |
| | | **Immediately EOI** | within +10 minutes after EOI |
| | | 2 hours after SOI | ± 15 minutes |
| | | 3 hours after SOI | |
| | | 4 hours after SOI | |
| 12-lead ECG | Day 1 | **1 hour after EOI**[1] | ± 15 minutes |

**Abbreviation: ECG= Electrocardiogram, EOI = End of infusion, SOI = Start of infusion**

1. Continuous monitoring can be performed until 1hour after EOI at the investigator's discretion.

For safety assessments other than hypersensitivity monitoring (Vital signs, physical examination, clinical laboratory tests, 12-lead ECG and post-infusion immunogenicity assessments), assessment time points and visit windows will be applied according to the Table 4. Pre-dose assessment for Immunogenicity will be collected prior to the infusion on Day 1.

Even if an assessment takes place using the given tolerance window, the consecutive assessment will be performed from the baseline time point.

The assessment that will be performed during the study are shown in the Table 4.

## Table 4. Schedule of Assessments

| Assessments | Screening | In-House Stay | | | Out-patient Visits | | | | | | | | | EOS[1] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day of Study Period | Day -21 to -2 | Day -1 | Day 1 | Day 2 | Day 3[2] | Day 4[2] | Day 8 | Day 15 | Day 29 | Day 43 | Day 57 | Day 71 | Day 85 | Day 99 |
| Visit window (day) | | | - | - | - | - | - | - | ± 1 | ± 1 | ± 1 | ± 3 | ± 3 | ± 3 |
| Informed consent | X | | | | | | | | | | | | | |
| Medical and medication history | X | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Inclusion / exclusion criteria[3] | X | X | | | | | | | | | | | | |
| Body weight & Height[4] | X | X | | | | | | | | | | | | X |
| Physical examination | X | X | | | X | | | | | | | | | X |
| Viral serology test[5] | X | | | | | | | | | | | | | |
| Drugs of abuse / alcohol / nicotine check[6] | X | X | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Clinical laboratory tests[7] | X | X | | | X | | X | X | | X | | X | | X |
| Vital signs[8] | X | X | X | | X | X | X | X | X | X | X | X | X | X |
| 12-lead electrocardiogram[9] | X | | | | X | | X | X | | X | | X | | X |
| Infusion of IMP | | | X | | | | | | | | | | | |
| Pharmacokinetic sampling[10] | | | X[11] | X | X | X | X | X | X | X | X | X | X | X |
| Hypersensitivity monitoring[12] | | | X | | | | | | | | | | | |
| Immunogenicity[13] | | | X[11] | | | | | X | | X | | X | | X |
| Restriction assessment | X | X | | | | | | | | | | | | |
| Concomitant medication[14] | X | X | | | | | | | | | | | | |
| Adverse events | X | X | | | | | | | | | | | | |

**Abbreviations: EOI = End of infusion, EOS = End of study, IMP = Investigational medicinal product, SOI = Start of infusion**

1. End-of-study visit procedures will be performed for subjects who completed the study as well as subjects who terminated the clinical study prematurely. After the EOS visit, serious adverse drug reactions will be reported to the Sponsor or its designee.
2. Assessments on Day 3 and 4 can be carried out either during the In-House Stay or on an out-patient basis according to Investigator decision.
3. Inclusion and exclusion criteria should be checked before randomization.
4. Height will be measured at screening only.
5. Serology tests will be performed at the screening visit for human immunodeficiency virus (HIV) -1 or -2 antibodies, hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb), hepatitis C antibody and syphilis.
6. Drug abuse testing includes the followings: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and cannabinoids during the screening period only. The history of Drug abuse, alcohol and nicotine will be checked by medical history taking by Investigator during the screening period and Day -1.
7. Clinical laboratory tests will be carried out at screening, on Day –1, Day 3, 8, 15, 43, 71, and 99; **Hematology** (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, and platelets), **Clinical chemistry** (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, total cholesterol, creatine phosphokinase, creatine kinase–myocardial band isoenzyme, creatinine, creatinine clearance [estimated by Modification of Diet in Renal Disease [MDRD]], C reactive protein, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, triglyceride, and Troponin I), **Urinalysis** (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination), **Coagulation** (Fibrinogen, international normalized ratio, prothrombin time, and activated partial thromboplastin time)
8. Vital signs will be measured at screening, on Day –1, before dosing on Day 1, on Day 3, 4, 8, 15, 29, 43, 57, 71, 85, and 99.
9. Twelve-lead ECG will be performed at the screening visit, on Day 3, 8, 15, 43, 71, and 99.
10. Blood samples for PK analysis will be collected as specified in **Table 2**.
11. Pre-dose blood sample for PK and immunogenicity assessment will be collected before start of infusion on Day 1.
12. For hypersensitivity monitoring, vital signs measurement and 12-lead ECG will be done as specified in **Table 3**.
13. Immunogenicity will be assessed on before dosing on Day 1, on Day 15, 43, 71 and 99.
14. Prior and concomitant medication use will be recorded for the 30 days prior to the screening visit until the EOS visit.

## 7.2 Assessments by Visit

### 7.2.1 Screening Visit (Days –21 to –2)

All screening assessments will be the same for subjects in all parts of the study (unless otherwise indicated).

Potential subjects for the inclusion in the study will be asked to attend the screening visit fasting apart from water (duration of the fast approximately 4 hours). Written informed consent will be obtained from all subjects before any screening procedures are performed. Subjects will be fully informed of their responsibilities (in terms of attending the study visits, dietary and lifestyle restrictions) of all the procedures expected to be performed in the study, the possible risks and disadvantages of being dosed with bevacizumab and their rights while participating in the study. They will have the opportunity to ask questions and have time to consider participation. If the subject wishes to participate in the study, they will be asked to sign and date the ICF.

The screening visit will take place within the 21 days prior to dosing (Day –21 to Day -2) unless otherwise approved by the Sponsor/Medical Monitor or Investigator. If more tests or assessments are required to check the subject's eligibility for study participation, a subject may be invited to additional visits within the screening period at the discretion of the Investigator.

During the screening visit, the following evaluations will be performed:

- Obtain written informed consent
- Medical and medication history
- Demographics: race, gender, age (years)
- Review inclusion/exclusion criteria
- Body height (cm), weight (kg), and BMI (kg/m$^2$)
- Physical examination
- Serology (hepatitis B, hepatitis C, HIV testing, and venereal disease research laboratory [VDRL] testing)
- Screen for drugs of abuse, the history of drugs of abuse, alcohol and nicotine
- Twelve-lead ECG
- Vital signs (BP, HR, BT, and RR)
- Clinical laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis)

- AEs, concomitant medications and restriction assessments

If in the opinion of the Investigator, the subject has any clinically significant abnormality, he will be excluded from the study.

### 7.2.2 In-House Stay (Day −1 to Day 2) and Out-Patient Visits (Day 3 to Day 85)

Subjects who successfully complete the screening visit will be domiciled in the study center as scheduled on Day –1. Inclusion and exclusion criteria will be reviewed to confirm subject eligibility on admission. Subjects will enter the study center for the in-patient stay on Day –1. If the subject is eligible, he will be randomized on Day –1.

Meals will be served during the in-house stay. The in-house stay will provide an enhanced level of subject supervision and safety; it will also facilitate the maintenance of compliance and ensure that all study procedures are completed at the appropriate time intervals. The subjects can be discharged from the clinical unit on Day 2 after all study procedures have been completed. Assessments on Day 3 and 4 can be carried out either during the In-House Stay or on an out-patient basis according to the Investigator decision. Thereafter, all study-related procedures and assessments will take place on an out-patient basis. Refer to Table 4 for a presentation of the single study procedures.

### 7.2.3 End-of-Study Visit (Day 99)

On Day 99, subjects will return to the clinical unit for an EOS visit. The following evaluations will be performed:

- Body weight
- Physical examination
- Clinical laboratory testing (hematology, clinical chemistry, coagulation and urinalysis)
- Vital signs (BP, HR, BT, and RR)
- Twelve-lead ECG
- PK sampling
- Sampling for immunogenicity against CT-P16, EU-approved Avastin and US-licensed Avastin
- AEs, concomitant medications and restriction assessments

### 7.2.4 Early Termination Visit

If a subject withdraws prematurely after dosing, all data normally to be collected at EOS (Section 7.2.3) will be collected at the time of premature discontinuation or at the scheduled EOS. If deemed necessary by the Investigator, then the subject will be asked to return at the regularly scheduled EOS visit.

## 7.3 Restrictions

### 7.3.1 Dietary and Fluid Restrictions

Alcohol: Alcohol consumption must be avoided from 48 hours before any study visit and while subjects are confined to the study center. Subjects will abstain from alcohol-containing products for 24 hours prior to each PK sample time point. Subject will not exceed an alcohol consumption of 7 units per week. One unit is equivalent to a half-pint (285 mL) of beer/lager, one measure (25 mL) of spirits, or one small glass (125 mL) of wine. The Investigator will check if subject is complying with these restraints.

Caffeine: Subjects will not be permitted to drink caffeine-containing products (e.g., coffee, black tea, cola) or use caffeine or xanthine-containing products for 48 hours prior to infusion of the investigational product and during the confinement period of the study. Subjects will abstain from caffeine-containing products for 24 hours prior to each PK sample time point.

Nicotine: Subjects will be permitted to smoke less than 10 cigarettes or equivalent per day until the end of the study period, but will not be allowed to smoke during the confinement period of the study.

Meals: Subjects must abstain from all food and drink (except water) at least 8 hours prior to the IMP infusion and at least 4 hours prior to any safety laboratory evaluations. Water is permitted until 1 hour prior to the SOI and may be consumed without restriction beginning 1 hour after the EOI. Lunch will be provided approximately 2 hours after the EOI. No outside food or drink is permitted at the study center. All meals and snacks will be provided by the study center.

### 7.3.2 Other Restrictions

Activity: Strenuous activity (e.g., heavy lifting, weight training, calisthenics, and aerobics) is prohibited from 96 hours prior to admission until discharge. After discharge, mild physical activity can be resumed, but strenuous physical activity is prohibited until EOS. Subjects will remain in a semi-recumbent position starting from administration of IMP until the EOI of the IMP. Measures are to be administered to minimize toilet visits (e.g., emptying bladder before infusion). In case the subject has to get up, he should call the study staff for assistance.

Medications: The use of herbal supplements is prohibited within 28 days prior to the study drug administration until EOS. Use of prescription, OTC medications, or dietary supplements is prohibited within 7 days or 5 half-lives (whichever is longer) prior to the study drug administration until EOS will not be permitted. For live or attenuated vaccines, the vaccination within 30 days prior to the dose of the IMP until EOS will not be permitted. Concomitant medication use is permitted if indicated by the Investigator for premedication or treatment of an AE.

Contraception: Men with childbearing potential female partner must agree to use a highly effective method of contraception throughout the study and for 6 months after the administration of assigned treatment. Subject is not permitted to donate sperm or plan to have a child within a 6-month period following IMP administration.

# 8. STATISTICAL METHODS

Statistical analyses will be performed using [redacted]. PK parameters will be calculated using Phoenix [redacted].

The statistical methods for this study will be described in a detailed SAP, which will be finalized prior to locking of the database.

Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report.

## 8.1 Study Population

### 8.1.1 Disposition of Subjects

The number and percentage of subjects entering and completing the clinical study will be presented by treatment.

### 8.1.2 Protocol Deviations

Deviations from the protocol, including deviations of inclusion/exclusion criteria will be assessed as “minor” or “major” in agreement with the Sponsor. Deviations will be defined prior to unblinding.

### 8.1.3 Analysis Populations

All-randomized population: The all-randomized population is defined as all randomly assigned subjects.

Safety population: The safety population will include all randomized subjects who received a complete or partial dose of IMP. Subjects will be included in the analysis according to the dose and IMP received. All safety analyses will be based on the safety population.

Pharmacokinetic population: The PK population will include all subjects who have received a complete dose of IMP with collection of at least one post-treatment PK sample. Subjects in the PK population will be analyzed according to the treatment they received.

## 8.2 General Considerations

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, standard deviation [SD], minimum, median and maximum). Categorical data will be summarized by treatment group using frequency tables (number and percentage).

Any outliers that are detected during the blind review of the data will be investigated. Methods for dealing with outliers will be defined in the SAP, prior to unblinding.

## 8.3 Safety Analyses

### 8.3.1 Adverse Events

Adverse events will be graded for intensity and the terminology of AEs will be described according to the CTCAE v4.03. All safety data will be listed and summarized by treatment group as appropriate. Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities.

The following TEAE summaries will be reported by system organ class, preferred term, and treatment group:

- The number and percentage of subjects reporting at least 1 TEAE
- The number and percentage of subjects reporting at least 1 TESAE
- The number and percentage of subjects leading to permanent discontinuation due to an TEAE
- The number and percentage of subjects with AESI

If more than 1 TEAE is recorded for a subjects within any system organ class or preferred term, the subject will be counted only once within the respective summary.

Adverse events will also be summarized by maximum intensity and relationship to IMP with the percentage of subjects in each category.

Adverse events of special interest will also be summarized by intensity.

### 8.3.2 Clinical Laboratory Tests

Clinical laboratory tests will be summarized by treatment group at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all post infusion scheduled collection times. All laboratory results will be listed.

### 8.3.3 Vital Signs

Vital signs will be listed and summarized, by treatment group at each scheduled collection time. Change from baseline will also be summarized for all post-infusion scheduled collection times.

### 8.3.4 Electrocardiogram

Overall assessment and ECG parameters will be listed and summarized by treatment group and visit. In addition, change from baseline in ECG parameters will be summarized by treatment.

### 8.3.5 Physical Examination

A shift table comparing the categorical results at each scheduled post-baseline visit with those at baseline will be summarized by treatment group and visit. All physical examination findings will be presented in a data listing.

### 8.3.6 Immunogenicity analysis

Immunogenicity will be summarized by treatment.

## 8.4 Pharmacokinetic Analyses

The PK analysis will be conducted on the PK population.

PK concentration data and parameters will be listed by subject including actual sampling times relative to dosing. Serum concentrations and parameters will be summarized by treatment. The following descriptive statistics will be presented for serum concentrations and parameters obtained at each nominal time point: n, mean, SD, coefficient of variation (CV), geometric mean, median, minimum and maximum values.

The non-compartmental PK parameters listed in Sections 3.2.1 and 3.2.2 will be calculated using [redacted] based on the following guidelines:

- $C_{max}$ will be obtained directly from the concentration-time data.
- $T_{max}$ is the time at which $C_{max}$ is observed.
- $\lambda_z$ will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

  - A minimum number of 3 data points in the terminal phase will be used in calculating $\lambda_z$ with the line of regression starting at any post-$C_{max}$ data point ($C_{max}$ will not be part of the regression slope) and including $C_{last}$ and $t_{last}$. The adjusted coefficient of determination ($R^2$ adjusted) in general should be greater than 0.85. All the derived parameters (i.e. $\lambda_z$, $t_{1/2}$, $AUC_{0\text{-inf}}$, CL, and $V_z$) will need to be flagged accordingly.
  - An appropriate number of decimal places will be used for $\lambda_z$ to enable the reported value of $t_{1/2}$ to be calculated.

- $t_{1/2}$ will be calculated as $\ln 2/\lambda_z$.
- $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ will be calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{0\text{-last}} = \int_0^t C(t)dt$ .
  - $AUC_{0\text{-inf}} = \int_0^t C(t)dt + \int_t^\infty C(t)dt = AUC_{0\text{-last}} + C_{last}/\lambda_z$.
  - $C_{last}$ is last observed quantifiable concentration.
- CL will be calculated as dose/$AUC_{0\text{-inf}}$
- $V_z$ will be calculated as $CL/\lambda_z$
- $\%AUC_{ext}$ will be calculated as $(1 - [AUC_{0\text{-last}}/AUC_{0\text{-inf}}]) \times 100$. The $\%AUC_{ext}$ should not exceed 20% for each individual profile. If the $\%AUC_{ext}$ is more than 20%, the individual result should be flagged as well as all parameters depending on $AUC_{0\text{-inf}}$. All the derived parameters (i.e. $AUC_{0\text{-inf}}$, $V_d$ and CL) will need to be flagged accordingly.

The statistical analysis of the log-transformed primary endpoints ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and $C_{max}$) will be based on an analysis of covariance (ANCOVA) model. The difference in least squares means between the CT-P16 and EU-approved Avastin, CT-P16 and US-licensed Avastin, and EU-approved Avastin and US-licensed Avastin, and the associated 90% CIs will be determined. Back transformation will provide the ratio of geometric means and 90% CIs for these ratios.

Similarity of systemic exposure ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and $C_{max}$) will be determined if 90% CI for the ratio of geometric means is within the acceptance interval of 80% to 125% for the following comparisons:

- CT-P16 vs EU-approved Avastin
- CT-P16 vs US-licensed Avastin
- EU-approved Avastin vs US-licensed Avastin

## 8.5 Interim Analyses

No formal interim analysis is planned.

## 8.6 Determination of Sample Size

This study is powered to demonstrate PK equivalence of CT-P16, EU-approved Avastin and US-licensed Avastin in $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and $C_{max}$. Assuming a CV of 30% and ratio of geometric means of 1.03, 42 subjects for each arm are needed to achieve 90% power for a 90% CI for the ratio of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and $C_{max}$ to satisfy the equivalence margin of 80% to 125%. The sample size is calculated from two one-sided tests with each 5% significant level using geometric mean ratio. A 10% dropout rate is anticipated so approximately 141 subjects (47 in each arm) will be enrolled.

# 9. DATA COLLECTION AND QUALITY ASSURANCE

## 9.1 Data Quality Assurance

The Sponsor or designee will conduct a study initiation visit to verify the qualifications of the investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. All information recorded in the eCRF for this clinical study must be consistent with the subject's source documentation. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to Good Clinical Practice (GCP) for compliance with applicable government regulations (ICH 2016). The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator.

## 9.2 Data Collection

Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized study site staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study subjects. The Investigator will ensure that the data collected are accurate, complete and legible.

The responsible study monitor will check data at the monitoring visits to the clinical study site. Data will be monitored within the eCRF by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within the eCRF.

All clinical work conducted under this protocol is subject to GCP regulations.

## 9.3 Case Report Forms and Source Documents

All data obtained during the clinical study will be promptly recorded in the eCRF. All source documents from which eCRF entries are derived will be placed in the subject's personal records.

The original eCRF entries for each subject will be checked against source documents by the monitor. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

## 9.4 Access to Source Documents

During the course of the study, a monitor will make clinical study center visits to review protocol compliance, compare eCRF entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. The eCRF entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the eCRF entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, competent authorities of certain countries and IRBs may wish to carry out source data inspections on-site, and the Sponsor's Clinical Quality Assurance Group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The Investigator assures the Sponsor of the necessary support at all times.

## 9.5 Data Management

Data management of all data documented will be performed under the responsibility of CRO or CELLTRION, Inc.

A Clinical Data Management Plan (CDMP) will be provided to the Sponsor describing the work and data flow within this clinical study which will be using an EDC System. The EDC System will be customized for this study. Both the EDC System and CDMP will be sent to the Sponsor for review and approval. The CDMP must be finalized before database lock.

For the EDC, a database structure that will host this study will be created and an interface to access it will be implemented. The system will establish and maintain the use of the computerized system according to the relevant SOP. Practical training sessions will be conducted on site to system users to teach them how to use the system.

Data will be collected individually in eCRFs. After all study materials are delivered and the eCRF is completed and validated, data will be entered in the clinical data storage system. Data will be available immediately to the data manager after it has been entered and therefore the data verification and validation process can start earlier contributing to data quality.

Any missing, implausible, or inconsistent recordings will be referred back to the Investigator using a data query form and will be documented for each individual subject before clean file is declared.

The AEs will subsequently be coded using the MedDRA, and prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

## 9.6 Archiving Study Documents

According to International Conference for Harmonization (ICH) guidelines, essential 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

# 10. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

## 10.1 Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP and the Declaration of Helsinki (WMA 2013). The clinical study also will be carried out in keeping with national and local legal requirements.

## 10.2 Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country and will be retained as part of the clinical study records. The Investigator will not undertake any investigation specifically required only for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

The Investigator must ensure that the subject received full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to withdraw from the study at any time without prejudice to future care. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

## 10.3 Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff, and receive IRB approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment but will also be mentioned in the integrated clinical study report. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

## 10.4 Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IB, and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number. Documents that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Investigator.

## 10.5 Liability and Insurance

The Sponsor will take out reasonable third party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator; the persons instructed by him/her and the hospital, practice, or institute in which they are employed; and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable laws and GCP guidelines.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

The method and manner of compensation to subjects should comply with applicable regulatory requirement(s).

## 10.6 Publication Policy

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator’s name, address, qualifications and extent of involvement.

An Investigator or CRO shall not publish, or present for publication any articles or papers or make any presentations, or assist any other person in publishing any articles or papers or making any presentations, or making any public declaration relating or referring to the clinical study, the results of the clinical study, in whole or in part, without the prior written consent of the Sponsor.

# 11. REFERENCE LIST

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