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ORIGINAL RESEARCH ARTICLE

A Randomized, Double-Blind, Parallel-Controlled Phase I Study Comparing the Pharmacokinetics, Safety, and Immunogenicity of SCT510 to Bevacizumab (Avastin®) in Healthy Chinese Males

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Abstract

Background SCT510 is a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), which is intended as a candidate biosimilar of bevacizumab that is approved for various metastatic cancers.

Objective This study aimed to compare the pharmacokinetics profiles, safety, and immunogenicity of SCT510 to bevacizumab (Avastin®) in healthy Chinese males.

Methods This was a single-center, double-blind, parallel-group phase I study. A total of 84 participants were randomly assigned (1:1) to receive a single 3 mg/kg infusion of either SCT510 or bevacizumab and followed up for 99 days. Primary endpoints were area under the serum concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), area under the serum concentration–time curve from time 0 to last quantifiable concentration (AUC_{0-t}), and the maximum observed concentration (C_{max}). Secondary endpoints included safety and immunogenicity.

Results A total of 82 subjects completed the study. Geometric means ratios (GMR) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 0.88, 0.89, and 0.97, respectively, for SCT510 versus bevacizumab (USA). The 90% confidence intervals for GMRs of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were all within the prespecified criteria (80–125%). No adverse events (AEs) led to study termination, and no serious adverse events (SAEs) were reported. None of the anti-drug antibodies (ADAs) identified were found to be neutralizing antibodies (NAbs), and only one subject from the SCT510 group tested positive for the ADA at the day 99 visit.

Conclusion This study demonstrated that the pharmacokinetics, safety, and immunogenicity of SCT510 were equivalent to bevacizumab (Avastin®). As a proposed biosimilar drug to bevacizumab, SCT510 was well tolerated in healthy Chinese males.

Clinical Trials Registration NCT05113511.

Key Points

Pharmacokinetics assessments of the originator with its proposed generic equivalent is an essential step in the clinical development of a potential biosimilar.

This phase I trial showed that SCT510 was pharmacokinetically comparable to the China-approved bevacizumab (Avastin®).

This study also demonstrated that SCT510 safety and immunogenicity were comparable to its reference product.

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1 Introduction

The vascular endothelial growth factor (VEGF), particularly VEGF-A, is a critical regulatory factor in driving tumor angiogenesis and is upregulated throughout many solid malignancies, and for this reason, blockade of the VEGF/its receptor (VEGFR) axis could impair blood vessel support and starve tumor of fuel and oxygen [1]. Over the past decades, antiangiogenesis therapy has proven to be an effective way to inhibit tumor development in solid tumors [2]. Neutralizing monoclonal antibodies, tyrosine kinase inhibitors, and soluble VEGF receptors, which work as decoy receptors, have been developed as anti-VEGF/VEGFR medicines [2, 3]. These drugs attack the tumor vascular microenvironment by blocking a specific link in the VEGF/VEGFR signaling pathway and show a spontaneous anti-tumor synergy. They have been used as "basic drugs" with chemotherapy or immunotherapy to expand indications, delay drug resistance, and improve patient survival.

Bevacizumab, known as the first antiangiogenic medicine, is a recombinant human monoclonal antibody that directly binds to circulating VEGF and inhibits the VEGF/VEGFR pathway. It has been shown to effectively restrict the number of new blood vessels while also inducing the regression of old tumor vasculature. The initial phase I research found that rhuMAb VEGF (bevacizumab) was well tolerated and safe in patients with advanced cancer without any dose-limiting toxicity after multiple dosages [4]. Bevacizumab injection (Avastin®) was licensed by the U.S. FDA in 2004 and by the EMA in 2006 and has been available in 134 countries [5]. Bevacizumab is currently considered a first- or second-line therapy for metastatic colorectal cancer, advanced or metastatic non-squamous non-small-cell lung cancer (NSCLC), advanced or metastatic renal cell carcinoma [6, 7], and advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer in combination with chemotherapy regimens [8, 9]. Furthermore, as a major antiangiogenesis biological agent, bevacizumab transformed the management of advanced solid organ malignancies, benefiting millions of patients worldwide. The treatment strategy for bevacizumab combined with chemotherapy in NSCLC has been alternated from the first-line position of chemotherapy [10]; bevacizumab in combination with atezolizumab has been utilized as first-line therapy for unresectable or metastatic hepatocellular carcinoma patients with superior overall and progression-free survival outcomes compared with sorafenib [11].

Biosimilars are biologic products that demonstrate structural similarity and biological function to their reference products approved by a regulatory agency. The development of biosimilars is not just for saving the cost of healthcare but also for new clinical treatment approaches and the balance of the biologics market [12, 13]. The expiration of patents on original biologic (hereinafter "reference product") renders them accessible to patients. For the bevacizumab originator, most key patent regulatory market exclusivities have expired [14]. A few bevacizumab biosimilars have been approved globally, with efficacy and safety characteristics that are quite equivalent to the reference medicine [15]. Thus, bevacizumab biosimilars have the potential to be widely used for tumor treatment.

SCT510, a recombinant humanized anti-VEGF monoclonal antibody, was developed as a bevacizumab injection (Avastin®) biosimilar with an identical amino acid sequence. Based on the high similarity in quality attributes to an approved product, the biosimilar should be comparable in pharmacokinetic profiles to the reference product and assessed by comparative nonclinical and clinical investigations [16]. A series of analytical similarity assessments confirmed consistent physicochemical properties and critical quality attributes between SCT510 and bevacizumab. Furthermore, preclinical studies of this proposed biosimilar also established a high degree of similarity to the reference product in terms of biological activity in vitro, pharmacodynamics in vivo, and head-to-head comparisons of pharmacokinetics, toxicokinetics, and immunogenicity in nonhuman primates. Thus, this phase I trial was initiated to explore whether SCT510 is a biosimilar to bevacizumab by evaluating their PK parameters and immunogenicity, safety, and tolerability in healthy Chinese males.

2 Methods

2.1 Subjects

The volunteers were healthy males between the ages of 18 and 45 years, with a body weight of 45–100 kg and a body mass index (BMI) of 19–25 kg/m^2. They were all in good physical condition, and no clinically significant disorders were observed after general medical examinations for body systems. Key exclusion criteria included participants with (1) known or suspected inherited bleeding propensity or coagulation dysfunction, (2) a history of thrombosis or bleeding, (3) a history of gastrointestinal perforation or gastrointestinal fistula, (4) prior use of any biological products or having been vaccinated with a live virus vaccine within the preceding 3 months, (5) any monoclonal antibody use within the last 12 months, (6) a history of anti-VEGF/VEGFR protein products or small-molecule drugs exposure within the past year. It is noteworthy that female participants were ineligible because of the potential

risk of ovarian failure and the long-term effects of bevacizumab on fertility [17].

2.2 Study Design

This single-dose, randomized, double-blind, parallel-controlled phase I study in healthy adult males was conducted between 9 May and 28 November 2018 in accordance with the biosimilar development guidelines issued by China's National Medical Products Administration (NMPA) [18, 19]. The protocol and other documents of this trial have been approved by the Medical Ethics Committee (EC) of the First Affiliated Hospital, Medicine School of Zhejiang University.

Following a successful screening, subjects were randomly (1:1) assigned to a single 3 mg/kg injection of either bevacizumab or SCT510. Subjects would be admitted to the research center on day 1 and would be allowed to leave on day 5 (96 h). According to this protocol, subjects were requested to return for 10 follow-up visits, namely on days 8, 15, 22, 29, 43, 57, 64, 71, 85, and 99 for pharmacokinetics and safety assessments.

2.3 Samplings and Assessments

Blood samples were collected on day 1 before dose administration, within 5 min after the end of infusion, and 4, 8, 24, 48, and 96 h after the start of the infusion, and on days 8, 15, 22, 29, 43, 57, 64, 71, and 85. Blood sampling points for immunogenicity were day 1 before infusion, and day 15 (336 h), day 29 (672 h), day 43 (1008 h), day 71 (1680 h), and day 99 (2352 h) after infusion completion.

For pharmacokinetics assessments, the total serum drug concentrations were measured by enzyme-linked immunosorbent assay (ELISA), while for immunogenicity, serum ADA and NAbs were detected by electrochemiluminescence (MSD). All immunoassays have been verified methodologically. Safety was assessed by (1) AEs including treatment-emergent adverse events (TEAEs), treatment-related treatment-emergent adverse events (TRAEs), and adverse events of special interest related to the study drug (AESIs); (2) vital signs; (3) physical examination; (4) laboratory tests; (5) 12-lead electrocardiogram (ECG). Any AEs or SAEs that occurred during this period should have been followed up until the participants recovered or the event was resolved. The number of participants with AEs was summarized, coded, and classified according to the Medical Dictionary for Regulatory Activities (MedDRA; version 20.0). AEs were graded according to Common Adverse Event Evaluation Criteria (CTCAE; version 4.03). Descriptive statistical analyses were applied.

2.4 Evaluation Endpoints

The primary endpoint was defined by the NMPA Guideline in 2016 [20] as the area under the concentration–time curve from time zero (pre-dose) extrapolated to the last quantifiable concentration (AUC_{0-t}). The secondary endpoints included maximum serum concentration (C_{max}), the time of maximum serum concentration (T_{max}), the area under the concentration–time curve from time zero (pre-dose) extrapolated to infinity ($AUC_{0-\infty}$), elimination rate constant of the drug (λ_z), half-life ($t_{1/2}$), clearance (CL), and the volume of apparent distribution (V_d).

2.5 Sample Size Determination

Based on an assumption of the coefficient of variation (CV%) 25% and GMR 0.95–1.05 (double one-sided $\alpha = 0.05$, test power $1-\beta = 0.90$), the study sample size was estimated as 37 for each group. Considering that a potential 10% drop out, 84 subjects (42 per group) were enrolled to satisfy the equivalence in the range of 0.8–1.25. Due to uncertainty in the initial CV estimate for the sample size determination, a two-stage adaptive design was used, allowing for a sample size adjustment based on the pharmacokinetic variability observed at an interim analysis. The interim analysis was performed blindly after 50% of the subjects had completed their follow-up visits. The interim analysis result (CV%) will be used to determine whether additional subjects are recruited. If CV% $\geq$ 25%, the sample size will be re-estimated.

2.6 Statistical Analysis

Pharmacokinetic analysis was based on the pharmacokinetic population. The serum drug concentration results were statistically calculated by Phoenix WinNonlin software (Pharsight Corporation, version 6.3). In this study, a non-compartmental model was used to construct the concentration versus time plot following a single dose of SCT510 or bevacizumab, which can provide information about the absorption and elimination characteristics and relevant PK parameters of the drug. Statistical phrases will be used to describe the unconverted data of PK parameters for analysis and summary.

The difference of $AUC_{0-t,}$ C_{max}, or $AUC_{0-\infty}$ between the two groups after logarithmic transformation was analyzed by using a variance analysis model. The GMR (test/control) and the 90% confidence intervals (CIs) were calculated by using the ANCOVA model and back-transforming the difference in geometric least-squares means. SCT510 would be considered biosimilar to bevacizumab if the 90% CIs for GMR of $AUC_{0-\infty}$, C_{max}, and AUC_{0-t} were within the bioequivalence margins of 80–125%.

All AEs were classified and rated according to the medical dictionary code system and the Common Adverse Event Evaluation Criteria (CTCAE; version 4.03) respectively. The incidence of all AEs was summarized by "the number of cases", and these AEs will be described by system organ classification (SOC), the preferred term (PT), and groups and calculated by Fisher's exact test. The positive rates of ADA and NAbs were also analyzed descriptively.

3 Results

3.1 Subject Disposition

A total of 289 volunteers were recruited for this study, of which 84 subjects were successfully enrolled and randomized (1:1) to the SCT510 group (42 cases) or the bevacizumab group (42 cases). Of the 84 participants, 2 did not complete the study: one from the SCT510 group withdrew before the dosage for stomach discomfort and low blood pressure, and the other who had accepted the bevacizumab withdrew voluntarily after the day 43 visit. Thus, 83 subjects who received the study drugs comprised the demographics, safety, and immunogenicity populations. 82 subjects (97.6%) who completed the entire trial were included in the pharmacokinetics population (Fig. 1).

3.2 Subject Demographics

The two groups were compared favorably across all baseline parameters. As shown in Table 1, all subjects were male, of which 76 cases (91.6%) were Han and 7 cases (8.4%) were from other ethnicities. Likewise, their mean age ranged from 19 to 43 years. Their mean (standard deviation) body weight and BMI in the SCT510 and bevacizumab groups were 63.7 (5.79) kg/m^2 and 22.3 (1.45) kg/m^2, respectively. No statistical difference was observed between the two groups.

3.3 Pharmacokinetics

82 subjects were included in the pharmacokinetic population. As shown in Fig. 2, the value of serum drug concentration at each time point was relatively close after a single 3 mg/kg administration of SCT510 or bevacizumab, and the mean serum drug concentration–time curve in each group matched similarly over the entire course of sampling. The PK parameters were summarized in Table 2. The results demonstrating the PK endpoints of SCT510 were comparable to the reference product.

Biosimilar analysis was shown in Table 3. For each of the key primary PK endpoints (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}), the 90% CIs of GMR were within the bioequivalent criteria (80–125%). In summary, the PK parameters of SCT510 and bevacizumab were highly similar, and SCT510 was bioequivalent to bevacizumab in terms of pharmacokinetics.

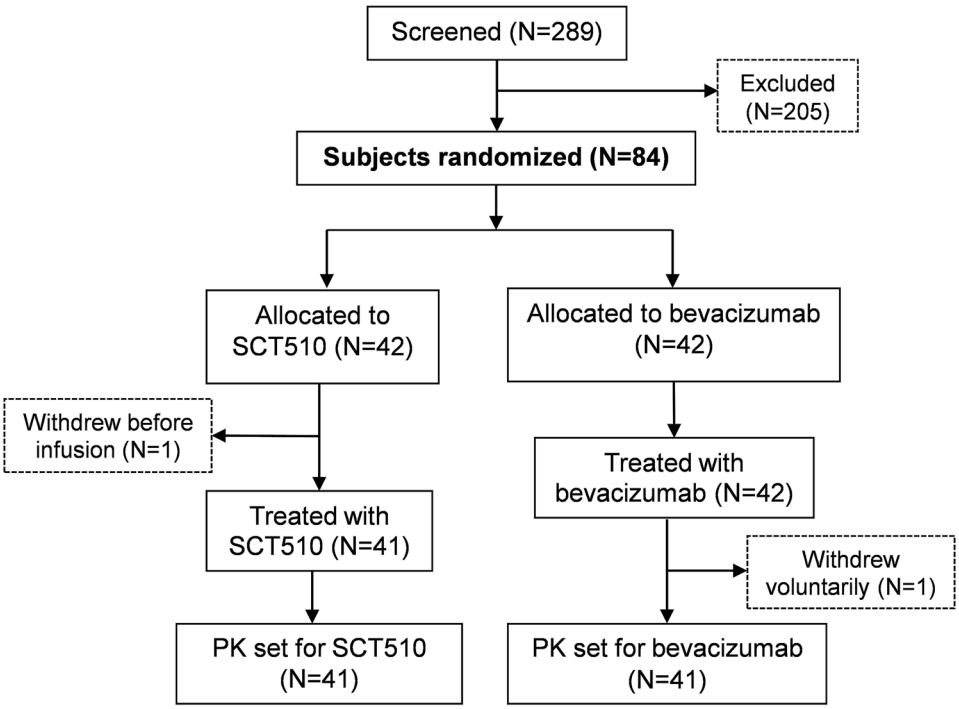

Fig. 1 Summary of subject disposition

Table 1 Summary of demographics and baseline characteristics

	SCT510 ($N = 41$)	Bevacizumab ($N = 42$)	Total ($N = 83$)
Age (years)			
Mean (SD)	27.7 (6.12)	30.1 (6.66)	29.0 (6.47)
Median (range)	27.0 (19–43)	29.0 (19–43)	28.0 (19–43)
Sex [*n* (%)]			
Male	41 (100)	42 (100)	83 (100)
Nationality [*n* (%)]			
Han	39 (95.1)	37 (88.1)	76 (91.6)
Other	2 (4.9)	5 (11.9)	7 (8.4)
Height (cm)			
Mean (SD)	169.4 (6.70)	168.6 (4.87)	169.0 (5.82)
Median (range)	168.0 (157–188)	167.0 (159–182)	168.0 (157–188)
Weight (kg)			
Mean (SD)	64.01 (6.366)	63.48 (5.223)	63.74 (5.786)
Median (range)	63.70 (52.1–77.9)	63.60 (53.8–76.3)	63.70 (52.1–77.9)
BMI (kg/m^2)			
Mean (SD)	22.27 (1.422)	22.32 (1.499)	22.29 (1.453)
Median (range)	22.23 (19.4–24.9)	22.23 (19.1–24.9)	22.23 (19.1–24.9)

BMI body mass index, *n* number of subjects, % percentage of subjects [calculated as 100 × (number of non-missing observations/number of subjects)], *SD* standard deviation

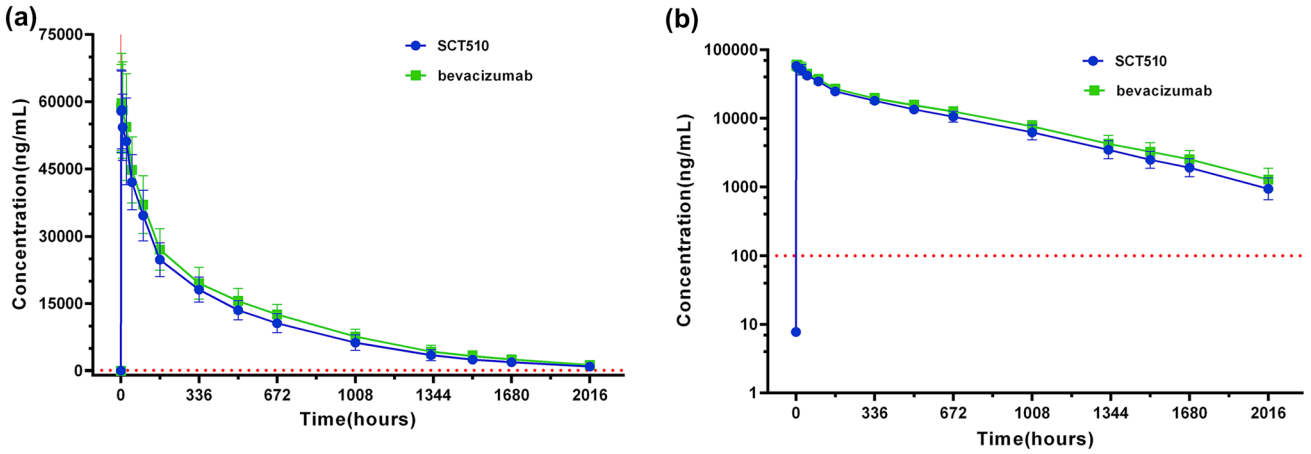

Fig. 2 Mean (±SD) serum drug concentration–time curve following a single intravenous dose of SCT510 ($N=41$) or bevacizumab ($N=41$) in healthy male subjects on (**a**) linear and (**b**) semi-logarithmic scales. Times are relative to the start of infusion. The dotted line in the figure is the lower limit of quantification (LLOQ), a value of 100 ng/mL

3.4 Safety

All AEs in this study were summarized in Table 4. In the safety population (all subjects who initiated treatment), the number (percentage) of participants who experienced AEs was 38 (92.7%) and 41 (97.6%) in the SCT510 group versus the bevacizumab group, respectively. The rates of TEAEs and TRAEs were 92.7% and 73.2% of the SCT510 group, while they were 97.6% and 78.6% in the bevacizumab group. The only Grade 3 TEAE (2.4%) possibly related to bevacizumab was sinus bradycardia (however, the patient recovered with no medication). Among the AESIs reported, 3 (7.3%) cases in the SCT510 versus 8 (19.0%) cases in the bevacizumab group included protein in the urine (7.3% versus 14.3%) and increased blood pressure (0 versus 4.8%). During the study, no deaths or discontinuations occurred because of AEs. There were no Grade 4 or 5 TEAEs, as well as no infusion reaction(s).

The reported AEs mainly involved laboratory examinations, cardiac disorders, infections and infestations, gastrointestinal diseases, and ocular diseases that were expected and similar to bevacizumab. As shown in Table 5, the most

Table 2 Pharmacokinetics parameters of SCT510 and bevacizumab (pharmacokinetic population)

Parameter (units)	SCT510 ($N = 41$)	Bevacizumab ($N = 41$)
AUC_{0-t} (h*μg/mL)		
Mean (SD)	20,504.4591 (2841.5520)	23,194.0633 (23,638.8648)
CV (%)	13.8582	15.6888
$AUC_{0-\infty}$ (h*μg/mL)		
Mean ± SD	21,038.9109 (3041.2731)	23,955.4465 (4015.0890)
CV (%)	14.4555	16.7607
C_{max} (μg/mL)		
Mean ± SD	61.643 (9.9201)	63.510 (11.7953)
CV (%)	16.0928	18.5724
λ_z (1/h)		
Mean ± SD	0.0019 (0.0003)	0.0018 (0.0004)
CV (%)	15.9615	19.0917
$t_{1/2}$ (h)		
Mean ± SD	376.0170 (60.0761)	390.2892 (69.2048)
CV (%)	15.9770	17.7317
CL (mL/h/kg)		
Mean ± SD	0.1457 (0.0221)	0.1286 (0.0210)
CV (%)	15.1880	16.3407
V_d (mL/kg)		
Mean ± SD	78.1487 (12.2612)	71.3676 (12.4844)
CV (%)	15.6895	17.4930
T_{max} (h)		
Median	4.000	4.000
Min, max	1.48, 24.00	1.47, 24.00

Table 3 Statistical comparison of the key pharmacokinetics endpoints (pharmacokinetic population)

Parameter (units)	Geometric least-squares means		GMR	90% CI	Power (%)
	SCT510 ($N = 41$)	Bevacizumab ($N = 41$)	SCT510/ bevacizumab		
AUC_{0-t} (h*μg/mL)	9.9188	10.0398	0.8860	(0.8390, 0.9357)	100
$AUC_{0-\infty}$(h*μg/mL)	9.9437	10.0706	0.8808	(0.8316, 0.9330)	100
C_{max} (μg/mL)	4.109	4.135	0.9745	(0.9153, 1.0376)	100

common TRAEs (reported ≥ 5%) among the two groups included blood triglyceride increased, sinus bradycardia, dental ulcer, protein in the urine, increased blood uric acid, folliculitis, and increased D-dimer. In addition, treatment-related abnormalities in laboratory tests, vital signs, physical examinations, and 12-lead ECGs were similar in each group.

3.5 Immunogenicity

A total of 83 participants were included in the immunogenicity testing sets, and blood samples were collected 1 day before and 15, 29, 43, 71, and 99 days after infusion. All subjects in the bevacizumab group tested negative for ADA. Only 1 (2.4%) participant in the SCT510 group had a positive ADA with a relatively low titer (1.0) at day 99, while the NAbs result was negative at the same time. The positive rate of ADAs between the two groups showed no significant difference ($P = 0.4940$).

4 Discussion

This phase 1 study was designed to evaluate the PK similarity between SCT510 and bevacizumab and characterize the safety profile of SCT510 in healthy males. The results showed that the PK parameters of SCT510 and bevacizumab were similar, and the 90% CIs for the GMR of the main endpoints (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) were within the predefined bioequivalent range (80–125%). In addition, the safety and immunogenicity assessments demonstrated that SCT510 was also comparable to bevacizumab with no clinically meaningful differences in TEAEs and ADA/NAbs

Table 4 Summary of adverse events (safety population)

Adverse events [*n* (%)]	SCT510 (*N* = 41)	Bevacizumab (*N* = 42)
All AEs	38 (92.7)	41 (97.6)
TEAE	38 (92.7)	41 (97.6)
≥ Grade 3 TEAEs	0 (0.0)	1 (2.4)
TRAE	30 (73.2)	33 (78.6)
≥ Grade 3 TRAEs	0 (0.0)	1 (2.4)
Sinus bradycardia	0 (0.0)	1 (2.4)
AESIs[a]	3 (7.3)	8 (19.0)
Protein urine present	3 (7.3)	6 (14.3)
Blood pressure increased	0 (0.0)	2 (4.8)
SAE	0 (0.0)	0 (0.0)

AEs adverse events, *TEAEs* treatment-emergent adverse events, *TRAEs* treatment-related treatment-emergent adverse events, *AESIs* adverse events of special interest related to the study drug, *SAE* serious adverse event

[a]AESI specified as one of the following: gastrointestinal ulcers and perforation, hemorrhages, thromboembolism, hypertension, posterior reversible encephalopathy syndrome, proteinuria, and infusion-related reaction

Table 5 The most common (≥ 5%) treatment-related treatment-emergent adverse events (safety population)

Most common TRAEs[a]	SCT510 (*N* = 41) *n* (%)	Bevacizumab (*N* = 42) *n* (%)
Blood triglyceride increased	11 (26.8)	10 (23.8)
Sinus bradycardia	8 (19.5)	11 (26.2)
Dental ulcer	4 (9.8)	3 (7.1)
Protein urine present	3 (7.3)	6 (14.3)
Blood uric acid increased	3 (7.3)	0 (0.0)
Folliculitis	2 (4.9)	4 (9.5)
D-dimer increased	1 (2.4)	3 (7.1)

TRAEs treatment-related treatment-emergent adverse events

[a]TRAEs reported by ≥ 5% of participants in any treatment group

incidence between the two groups. In conclusion, SCT510 was shown to be biosimilar to bevacizumab in healthy Chinese male subjects after a single intravenous injection.

This study was set up as a parallel-group design instead of a cross-over design due to the long half-life (approximately to 20 days) of and the likelihood of developing immunogenicity to bevacizumab [4]. As a result, the study duration was set at roughly 4 half-lives (approximate to 85 days) to accurately describe the PK characteristics of the research medicines. However, the immunogenicity and incidence of AEs were continually explored until about 5 half-lives. The PK characteristics of bevacizumab were reported to be linearly related to the dosage ranges of 1–10 mg/kg [4]. The two dosage intensities of bevacizumab marketed in the USA and Europe were 2.5 mg/kg/week dose equivalent and 5 mg/kg/week dose equivalent [4, 21]. Therefore, a single dose of 3 mg/kg was selected for authentic and meaningful PK parameters and to reduce reducing drug exposure to healthy volunteers.

In this study, the PK profiles of STC510 were suggested to be similar to bevacizumab with an acceptance criterion of 80–125% following a single dose of 3 mg/kg. The mean $t_{1/2}$ (15 days) for STC510 was similar to that of the reference product, which was consistent with the $t_{1/2}$ reported in another bevacizumab study in healthy volunteers [22–24]. According to reports, this antibody has a small inter-CV among Chinese patients, but a large volume of distribution and a 14- to 16-day half-life [25–28]. A similar pattern of elimination for STC510 was also observed in this study, beginning with a rapid blood clearance stage lasting about 7 days, and then followed by a gradual clearance phase. The PK data of bevacizumab was collected from the Asian (Chinese) population, and the results were similar to those acquired from other nationalities [23, 27, 29], suggesting that no influence of race has been observed on the PK of bevacizumab. Hence, it is important to conclude that the results presented in this manuscript can be generalized to other regions than China.

According to this study, the reported AEs in the two groups were expected and comparable, which mainly involved laboratory examinations, cardiac disorders, infections and infestations, gastrointestinal diseases, and ocular diseases. All of the TRAEs are expected in the instructions of bevacizumab and are similar to other clinical trials [26, 30, 31].

We expect that the safety and pharmacokinetic profiles from this trial will offer valuable information for SCT510 further clinical practices. However, due to the limited sample size and the features of the subjects (all males) in this study, the administration and long-term efficacy of SCT510 need to be further explored. Furthermore, Phase II/III studies are being conducted in China to assess the efficacy, safety, and immunogenicity of SCT510 in patients with non-squamous cell non-small-cell lung cancer and hepatocellular carcinoma. It is believed that these SCT510 clinical studies will provide more PK profiles and safety information in the near future.

5 Conclusions

Based on the results of PK analysis, SCT510 and the original drug bevacizumab are bioequivalent in healthy Chinese male subjects. The safety analysis results show that the safety and immunogenicity of SCT510 are comparable to those of the

original drug bevacizumab, and SCT510 is safe and well tolerated in healthy Chinese men.

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Declarations

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Conflict of interest Dr. Liangzhi Xie is employee of Sinocelltech Ltd. and has ownership or potential stock option interests in the company. All authors declare no other conflicts of interest.

Ethical approval The final study protocol was approved by the ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine (approval NO. 2017-EC-244). All procedures involving subjects were strictly carried out according to Helsinki Declaration, the national Good Clinical Practice (GCP), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and all applicable regulatory requirements and laws. Before any procedures were performed, subjects signed written informed permission and were allowed to withdraw from the study at any moment.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability The original information in this article that supports the study conclusions is publicly available. All reasonable inquiries related to this study are welcomed.

Code availability Not applicable.

Author contributions Jianzhong Shentu and Liangzhi Xie were involved in the study's conception, design, and planning. Guolan Wu, Huili Zhou, Chang Xu, Lihua Wu, and Jingjing Zhang were all involved in the clinical trial's execution, data collection, and interpretation. Duo Lv was in charge of the research project's quality control. Jing Wu and Guolan Wu were responsible for data analysis, findings interpretation, and manuscript drafting. All authors have reviewed the manuscript substantially and agreed to submit the final version.

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