An Open-Label, Phase II Study to Evaluate the Efficacy and Safety of SCB01A in Subjects with Recurrent or Metastatic Squamous Cell Head and Neck Cancer Who Have Failed Platinum-Based Treatment

Protocol Number:	SCB01A-22
Investigational Product:	SCB01A
Development Phase:	Phase II
Version/Date:	Version 1.0 /19-Dec-2016
Sponsor:	SynCore Biotechnology Co., Ltd. No. 84 Chung-Shan Rd., Chung-Shan Village, Tung-Shan Shine, ILan, Taiwan, R.O.C.
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PROTOCOL APPROVAL PAGE

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INVESTIGATOR SIGNATURE PAGE

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INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by SynCore Biotechnology. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please retain the original for your study files.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: SynCore Biotechnology Co. Ltd.	
Name of Study Product: SCB01A	
Protocol Number: SCB01A-22	**Indication:** Recurrent or metastatic squamous cell carcinoma of head and neck
Title of Study: An open-label, phase II study to evaluate the efficacy and safety of SCB01A in subjects with recurrent or metastatic squamous cell head and neck cancer who have failed platinum-based treatment	
Study Center(s): Up to 4 centers in Taiwan	**Study Development Phase:** Phase II
Planned Number of Subjects: Up to 37 subjects will be enrolled, consisting of 10-13 subjects in Stage I and 19-24 subjects in Stage II, with replacement for those non-per protocol (non-PP) subjects (estimated 20% dropout rate).	
Study Rationale: From pre-clinical pharmacology and phase I clinical study SCB01A has demonstrated promising anticancer action with a vascular disrupting activity that has the potential for treatment of various malignancies, particularly for patients with drug resistance. The drug has been studied in human subjects in a dose-escalation phase I study and has shown to be safe for up to 2 cycles of 24 mg/m^2 (each cycle consisting of one intravenous [i.v.] administration of SCB01A via a central line every 3 weeks). In the phase I study, partial response (PR) (shrinkage of tumor size to 50%) was observed in cycle 9 (3 mg/m^2) of one subject with right buccal squamous cell carcinoma and 19/33 (58%) subjects had stable disease (SD) for more than 2 cycles. Pre-clinical study of SCB01A showed that the concentrations at which tubulin inhibition occurred were around 80 nM for 24-hour exposure or 200 nM for 6-hour exposure. However, pharmacokinetic (PK) results of phase I study showed that the average elimination half-life ($t_{1/2}$) of a 3-hours i.v. infusion of SCB01A is approximately 2.5 hours and almost no SCB01A can be detected after 10 hours, indicating most subjects were treated in short API exposure time and may have been insufficient to achieve efficacy. Therefore, to extend the exposure duration above effective concentration in blood may increase the treatment efficacy. The aim of this study is to evaluate the efficacy and safety of i.v. infusion for 24-hour of SCB01A in subjects with squamous cell carcinoma of head and neck who have failed previous platinum based therapies.	
Objectives: This is a Phase II study with intra-subject dose escalation to evaluate the efficacy and safety of SCB01A in subjects with recurrent or metastatic squamous cell carcinoma in head and neck. ***Primary Objective:*** To assess the objective response rate (ORR) during treatment phase according to the Response	

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Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Secondary Objective:

- To evaluate the safety and toxicity profile of SCB01A.
- To assess the overall survival (OS) after first treatment with SCB01A.
- To assess the progression-free survival (PFS).
- To assess the best overall tumor response after treatment with SCB01A.
- To assess the PK profile.

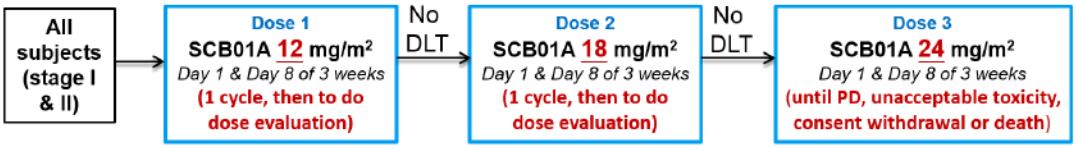
Trial Design:

Multicenter, open-label, phase II study of SCB01A administered to subjects with recurrent or metastatic squamous cell carcinoma of head and neck.

Intra-Subject Dose Escalation

All subjects enrolled in this study will be treated from the same starting dose 12 mg/m^2 (Dose 1) given on Days 1 and 8 in a 21-day cycle by 24 h IV infusion. If the subject experiences no dose-limiting toxicity (DLT) during the period, dose escalation of SCB01A to 18 mg/m^2 (Dose 2) occurred from Cycle 2; and increased to 24 mg/m^2 (Dose 3) on Cycle 3 (Figure 1).

Figure 1: Intra-Subject Dose Escalation



Dose modification

If the subject experiences a DLT at a given dose level, dose escalation will be halted and a reduced dose will be given to the subject. Dose adjustments were allowed based on the toxicity, efficacy evaluation, and clinical judgement by physician.

Rules for dose modifications of the study (Figure 2) are listed as following:

1. Dose 1 (12 mg/m^2), will be the starting dose regimen for all subjects. Safety and clinical benefit observation will be performed prior to drug administration on Cycle 2 Day 1.
   a) Dose de-escalation: if any DLT experienced before Cycle 1 Day 8, the dose will be de-escalated to Dose 1a (9 mg/m^2) for Cycle 1 Day 8. If first DLT during Cycle 1 is experienced after Cycle 1 Day 8, the dose will be de-escalated to Dose 1a (9 mg/m^2) for Cycle 2. If no DLT is observed in Dose 1a, the subjects will receive the Dose 1a until PD, consent withdraw or death. Once more dose de-escalation (Dose 1b, 7 mg/m^2) will be allowed if another DLT is observed in Dose 1a.
   b) Dose maintained: If clinical benefit observed at Dose 1 and without DLT, the dose level can be maintained until PD, intolerable toxicity, consent withdraw or death.
2. Dose 2 (18 mg/m^2), will be administrated for one cycle and safety and clinical benefit observation will be performed prior to drug administration on Cycle 3 Day 1.

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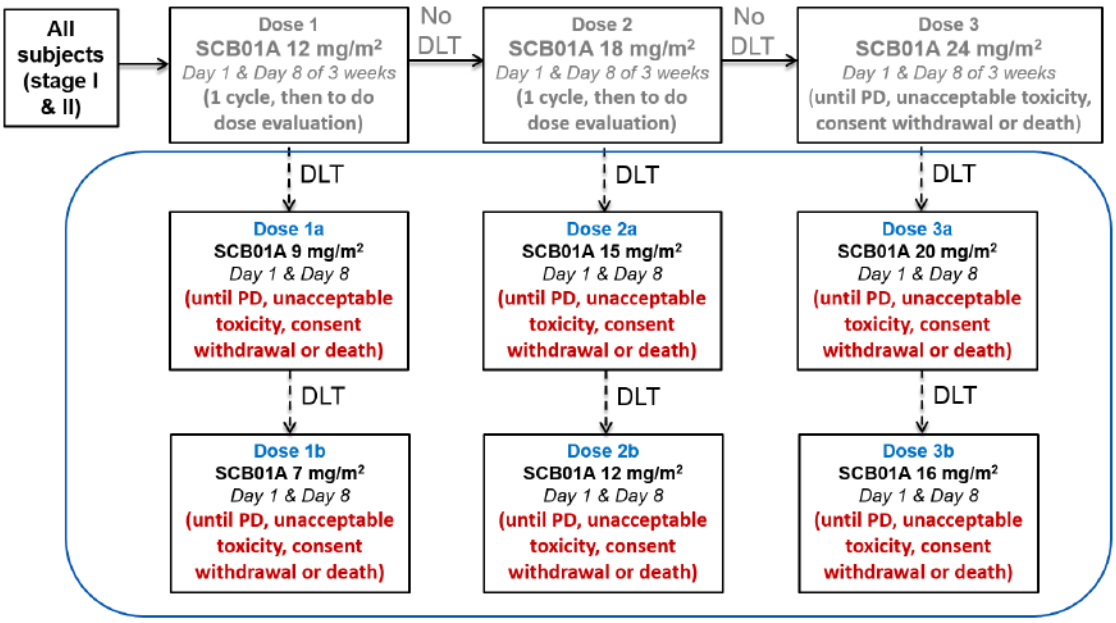
a) Dose de-escalation: if any DLT experienced before Cycle 2 Day 8, the dose will be de-escalated to Dose 2a (15 mg/m^2) for Cycle 2 Day 8. If first DLT during Cycle 2 is experienced after Cycle 2 Day 8, the dose will be de-escalated to Dose 2a (15 mg/m^2) for Cycle 3. If no DLT is observed in Dose 2a, the subjects will receive the Dose 2a until PD, consent withdraw or death. Once more dose de-escalation (Dose 2b, 12 mg/m^2) will be allowed if another DLT is observed in Dose 2a.

b) Dose maintained: If clinical benefit observed at Dose 2 and without DLT, the Dose 2 can be continued until PD, intolerable toxicity, consent withdraw or death.

3. Dose 3 (24 mg/m^2), will be administrated for one cycle and safety and tumor assessment will be performed prior to drug administration on Cycle 4 Day 1.

a) Dose de-escalation: if any DLT experienced before Cycle 3 Day 8, the dose will be de-escalated to Dose 3a (20 mg/m^2) for Cycle 3 Day 8. If first DLT during Cycle 3 is experienced after Cycle 3 Day 8, the dose will be de-escalated to Dose 3a (20 mg/m^2) for Cycle 3. If no DLT is observed in Dose 3a, the subjects will receive the Dose 3a until PD, consent withdraw or death. Once more dose de-escalation (Dose 3b, 16 mg/m^2) will be allowed if another DLT is observed in Dose 3a.

Figure 2: Dose Modification



If the subject experienced any neurotoxic DLT, the subject will be withdrawn.

Per-protocol (PP) subjects will be considered to be evaluable for ORR conclusion; Non-evaluable subjects will be replaced.

Simon's Two-Stage Design[1]

Stage I: A total of up to 10 evaluable subjects will be enrolled for Stage I to receive at least 3 cycles of i.v. administration by 24-hours infusion of SCB01A. The tumor response review will be

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performed with the subjects who completed 3 cycles of SCB01A treatment. If at least one response (CR or PR) is observed, another 19 evaluable subjects will be enrolled into Stage II.

Stage II: 19 evaluable subjects will be enrolled at stage II and treated with the same intra-subject dose escalation regimen from starting dose 12 mg/m^2. The tumor response review will be performed with the subjects who completed 3 cycles of SCB01A treatment.

All subjects will be treated until the occurrence of progressive disease, intolerable adverse events (AEs)/toxicity, consent withdrawal or death. After discontinuation of study treatment, all subjects will be followed for survival and disease-specific therapies of the clinician's choice will be administered. Follow-up visits will be scheduled every 3 weeks for 9 weeks (i.e. week 3, week 6, and week 9), thereafter every 9 weeks until the end of the study (either 12 months after the 1st treatment with SCB01A or end of 27 weeks survival follow-up, whichever comes later).

Data and Safety Monitoring Board (DSMB)

The DSMB, composed of medical monitors (physicians experienced in oncology studies) and at least one statistician, Their responsibilities are to review and evaluate the data for safety, study conduct and progress, and make recommendations concerning the continuation, modification, or termination of study. Serial assessments of PK results also may be taken into account for safety evaluation. A neurologist will be invited to join DSMB meeting as a consultant when neurotoxicity occurred.

The document review or meeting of DSMB will be held when the following scenarios:

- A subject is not recovered from Grade 2 neurotoxicity over three weeks;
- A subject revealed Grade 3 or above neurotoxicity;
- After 10 evaluable subjects finished the study in Stage I

Duration of Treatment:

- **Screening Period:** Up to 4 weeks
- **Treatment Period:** Study subjects will receive monotherapy of SCB01A until disease progression, intolerable toxicity, consent withdrawal, or death, whichever occurs first.
- **Follow-Up Phase:** 27 weeks (± allowed windows)

Total Study Duration: Around 52 weeks

Inclusion Criteria: Subjects are required to meet all of the following criteria for enrollment into the study.

1. Aged ≥20 years;
2. Signed informed consent obtained prior to initiation of any study-specific procedures and treatment;
3. Histological or cytological confirmed squamous cell carcinoma of head and neck, excluding nasopharyngeal carcinoma;
4. Subjects with unresectable, unfeasible radiotherapy, recurrent or metastatic head and neck squamous cell carcinoma, after previous treatment with platinum agent;

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5. Subjects must have at least one measurable tumor lesion as defined by RECIST version 1.1 as assessed by the investigator (local radiological image assessment) or clinically evaluable disease. Physical and neurological examinations, and radiographic studies have to be performed within 28 days of Cycle 1 Day 1;
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1;
7. Life expectancy of 12 weeks or longer;
8. Concurrent local therapy is not allowed, but concurrent palliative radiation therapy to non-measurable sites of disease such as painful bone metastasis is permitted;
9. All eligible subjects of childbearing potential have to use effective contraception; that is, double barrier contraceptive methods;
10. Documented progressive disease within past 6 months;
11. Adequate bone marrow reserve, cardiac, renal and liver function:
    a) Absolute neutrophil count (ANC) > 1.5 x 10^9/L;
    b) White blood cell (WBC) > 3 x 10^9/L;
    c) Platelet count > 75 x 10^9/L;
    d) Hemoglobin > 9 g/dL (> 5.6 mmol/l);
    e) Prothrombin time (PT)/international normalized ratio (INR) ≤1.5 x upper limit of normal (ULN);
    f) Creatinine clearance (Cockcroft & Gault formula) >50 mL/min;
    g) Alanine aminotransferase (ALT, SGPT) and aspartate aminotransferase (AST, SGOT) and Alkaline Phosphatase (ALP) < 3 x ULN; AST/ALT ≦ 5 x ULN if liver metastasis;
    h) Serum albumin ≥ 3 g/dL;
    i) Total Bilirubin ≤ 1.5 x ULN;
    j) QTc <450 msec

Exclusion Criteria: Subjects meeting any of the following criteria will be excluded from the study.

1. Known primary CNS malignancy or CNS involvement (except for brain metastases that have been treated and are stable and subject is off steroids);
2. Chemotherapy, radiation therapy, major surgery or investigational agents including immune or target therapies less than 4 weeks prior to study drug treatment;
3. History of malignancy other than head and neck cancer with the exception of early stage non-melanoma skin cancer or carcinoma *in situ* of cervix;
4. History of liver cirrhosis;
5. Active hepatitis B or hepatitis C infection;
6. Clinical significant pulmonary obstructive or clinical significant pulmonary restrictive diseases (grade >2);
7. Clinically significant cardiac disease (NYHA class > 2);
8. Other serious illness or medial conditions, such as active infection, unresolved bowel

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obstruction, or psychiatric disorders;

9. Known HIV positivity;
10. Pregnant or breast-feeding subjects, and men and women of child-bearing potential not using effective contraception while on study treatment;
11. Known hypersensitivity to any component of SCB01A or excipients including Solutol®, alcohol, and PEG300;
12. History of exposure to SCB01A or its analogues;
13. History of active or significant neurological disorder or psychiatric disorder that would prohibit the understanding and giving of informed consent, or would interfere with the clinical and radiological evaluation of central nervous system during the trial;
14. Peripheral neuropathy (≥ grade 2);
15. Any other reason the investigator deems the subject to be unsuitable for the study.

Endpoints:

Primary endpoint:

- Objective response rate (ORR), defined as complete response (CR) + partial response (PR), according to RECIST v1.1 criteria

Secondary endpoints:

- Progression free survival (PFS)
- Overall survival (OS) after first treatment with SCB01A
- Best overall tumor response after treatment with SCB01A
- Safety: The safety endpoints used to achieve the secondary objectives of this study are:
  - Hematology, clinical chemistry, coagulation factors and urinalysis laboratory data changes
  - AE/SAE incidence
  - Physical examination result changes
  - Vital sign changes
  - Electrocardiogram (ECG) (including PR, QRS, QTc intervals) results

PK: Maximum plasma concentration [C_{max}], clearance [CL], volume of distribution [Vd], half-life [$t_{1/2}$], elimination constant [K_{el}], mean residence time [MRT] and time to maximum concentration [T_{max}])

Criteria for Evaluation:

Efficacy measurements:

Tumor Measurement: Tumor response will be assessed by using computerized tomography (CT) or MRI scans according to RECIST v1.1 at baseline, end of the first 3 cycles, and every three cycles thereafter until progression of disease. For subjects who meet objective response criteria after the first 3 cycles of study treatment, confirmative radiological tumor assessments will be performed at least 4 weeks later.

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Scans must include brain, chest, abdomen, and pelvis. The imaging technique used at baseline should be used throughout the study.

- ORR is defined as the percentage of subjects who have achieved confirmed CR and PR during treatment phase, according to RECIST v1.1. Not-confirmed CR or PR, or withdraw for DLT are counted as non-responder.
- PFS is defined as the time from the start of treatment up to the date of first progression based on RECIST v1.1 or the date of death, whichever comes first.
- OS is defined as the time from the start of treatment up to the time that the subject is still alive.
- Best overall tumor response defined as the best response from start of treatment through all treatment phase or until disease progression/recurrence.

Survival data will be collected throughout the active treatment phase and during the 27 weeks follow-up period. Survival follow-up after subject discontinuation of treatment will be conducted every 3 weeks during the first 9 weeks, thereafter every 9 weeks until the end of the study to assess for survival. Survival rate will only be assessed in subjects with measurable disease at baseline.

Dose Limiting Toxicity (DLT):

All toxicities will be classified according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) version 4.03. DLT will be defined as the occurrence of any of the following criteria unless there is definitive alternative evidence that administration of SCB01A did not cause the specific toxicity:

- Grade 4 neutropenia exceeding 5 days' duration;
- Grade 4 thrombocytopenia;
- Grade 4 anemia;
- Grade 3 or greater neutropenia with complications (e.g., fever, infection etc.);
- Grade 3 or greater thrombocytopenia with complications (e.g., bleeding);
- Grade 3 or greater non-hematological AEs including Grade 3 unmanageable nausea and vomiting that persist for 3 or more days after drug administration. Grade 3 fatigue lasting for ≤1 week is not considered as a DLT;
- Grade 3 or greater prolonged QTc interval;
- Grade 3 or greater neurotoxicity;
- Delayed treatment exceeding 14 days duration due to drug-related toxicity;
- Not able to recover from grade 2 neurotoxicity exceeding 3 weeks.

Safety measurements:

The following safety assessments will be done during the study:

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- Incidence and intensity of AEs evaluated using the CTCAE version 4.03
- Incidence and intensity of clinically significant abnormal laboratory values evaluated using the CTCAE version 4.03
- Percentage of subjects experiencing dose modifications including delays or omissions or discontinuation of study medication
- Physical examination findings
- Neurological examination findings
- Vital signs measurements
- ECG (including PR, QRS, QTc intervals) findings
- Nerve conduction velocity examination (baseline for all subjects; symptom occurring and end of the study for subjects with grade 2 or greater neurological symptom)

PK measurements:

PK will be performed on subjects enrolled in stage I.

- PK blood samples will be taken immediately pre-infusion then at 24, 25, 26, 28, and 32 hours after the start of infusion on Days 1 and 8 of Cycle 3 if dose level of Cycle 3 is 24 mg/m^2(time window at each sample collected: ±5 min).

Statistical Considerations:

Populations for Analysis

Study subjects will be categorized into the following populations for analysis:

- **Intention-to-treat (ITT) population:** The ITT population consists of all subjects enrolled in the study and received at least one study treatment.
- **Per-protocol (PP) population:** The PP population will consist of all subjects who (1) withdraw from study for DLT, or (2) completed at least 3 cycles of study treatment regimen, have measurable baseline disease and, at least, one post-baseline RECIST assessment (PD, SD, PR or CR). Subjects with a major protocol deviation or AE, deemed by the Medical Monitor to have an impact on the study endpoints, will be excluded from the PP population.
- **PK population:** The PK population will consist of all subjects in stage I who received, at least, one dose of 24 mg/m^2 of SCB01A with sufficient post-dose bio-samples collected for PK profile characterization.

Details of any other populations for analysis will be described in the statistical analysis plan (SAP).

Statistical Analysis

Assumption of sample size calculation:

- Study design: Simon's two stage design
- Type I error (one-sided): 5%
- Power: 80%

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- Response probability of null hypothesis (P0): 0.05
- Response probability of SCB01A (P1): 0.20

According to these hypotheses, up to 37 subjects need to be recruited into the study (including 10 evaluable subjects in the Stage I and 19 evaluable subjects in Stage II, with the additional 8 subjects to account for replacement of subjects those who withdraw, i.e. dropout rate is 20%). At least 4 subjects are required to achieve CR or PR after treatment with SCB01A for the study to meet its primary objective. The trial will be discontinued if no objective response is observed after the Stage I tumor assessment review.

Stopping rule: stopped early for futility if less than 1/10 evaluable subjects showed ORR in Stage I; with no further investigation of the drug is less than 4/29 evaluable subjects achieve ORR by the end of Stage II.

Both according to ITT and PP approaches will be included in the efficacy analyses. The efficacy conclusion will be summarized according to analyses of PP population. Safety analysis will be done on ITT population. Inferential analysis results will be expressed as point estimates and their 95% confidence intervals (CIs). Analyses will be carried out using SAS® Software, version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

All time-to-event endpoints, including OS and PFS, will be reported in days (median with 95% CI and range) and calculated using Kaplan-Meier methods. Subjects who have not progressed or who have not died at the time of the analysis will be censored at the last assessment date.

PK Evaluations

The blood samples will be assayed for SCB01A and PK parameters (maximum plasma concentration [C_{max}], clearance [CL], volume of distribution [V_d], half-life [$t_{1/2}$], elimination constant [K_{el}], mean residence time [MRT] and time to maximum concentration [T_{max}]) will be determined and presented graphically and descriptively (as appropriate).

A detailed SAP will be finalized prior to final database lock. Any significant changes to the analyses described in this protocol will be addressed in the SAP and the Clinical Study Report.

Duration of the Study

The planned duration of the entire study is approximately 26 months with an enrollment period of 12 months.

End of Study

End of study will be either 12 months after the 1st treatment with SCB01A or end of 27 weeks survival follow-up, whichever comes later.

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FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse Event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
BSA	Body Surface Area
Ck	Creatine Kinase
CL	Clearance
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
HDL	High-density Lipoprotein
HPLC/MS-MS	High-Performance Liquid Chromatography/Tandem Mass Spectrometry
Hct	Hematocrit
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio

Abbreviation	Definition
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
K_{el}	Elimination Constant
LDL	Low-density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MTD	Maximum Tolerated Dose
NCV	Nerve Conduction Velocity
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PP	Per-Protocol
PR	Partial Response
PT	Prothrombin
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
Rx	Administration of SCB01A
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
T_{max}	Time to Maximum Concentration
ULN	Upper Limit of Normal
V_d	Volume of Distribution
WBC	White Blood Cell

Table 1: Study Schedule, Screening, and Treatment Phase

Study Visit[1]	Screening	Cycle 1				Cycle 2			Cycle 3			EOT[1] [2]	Early Withdrawal	Unscheduled
		C1D1		C1D8	C1D15	C2D1	C2D8	C2D15	C3D1	C3D8	C3D15			
		PreRx	PostRx											
Study Days	**-28 to -1**	**1 (±0)**		**8 (±1)**	**15 (±2)**	**22 (±1)**	**29 (±1)**	**36 (±2)**	**43 (±1)**	**50 (±1)**	**57 (±2)**	**64 (±2)**	**NA**	**NA**
Study Weeks		**0**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**NA**	**NA**
Activities														
Informed Consent	X													
Medical History	X	X												
Demographics	X													
Eligibility Criteria	X													
Physical Examination	X	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA Calculation		X		X		X	X		X	X				
ECOG Performance Status	X	X		X	X	X	X	X	X	X	X	X	X	X
Adverse Events Review[3]			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X[4]	X[4]	X[4]		X[4]	X[4]		X[4]	X[4]		X	X	X [13]
Radiological Image Assessments[5]	X											X	X	X [13]
Laboratory Assessments[6]	X	X[8]		X	X	X	X	X	X	X	X	X	X	X [13]
Urinalysis[7]	X	X[8]				X			X			X	X	X [13]
PK Blood Sample Collection [9]									X	X				
Serum Pregnancy Test [10]	X													
Study Drug Administration [11]		X		X		X	X		X	X				
Nerve Conduction Velocity [12]	X													

[1] Subjects may continue treatment beyond 3 cycles (9 weeks) of SCB01A treatment per investigator discretion if they are experiencing clinical benefit, until the study is terminated. Refer to Table 2 for the schedule of assessments for additional treatment cycles.

[2] EOT visit should be conducted 14 or 21 days (±2 days) after last infusion, depending on last infusion was given on Day 8 or Day 1, respectively. Early withdrawal visit should be conducted after the subject received the last dose of study treatment. A toxicity follow-up (can be done by phone contact) should be performed 28±3 days after the last dose of study treatment.

[3] All AEs including SAEs must be reported from the time of start of study treatment and must continue to be followed for 28 days after last administration of study treatment.

[4] ECG will be performed prior to study drug administration (pre-infusion), and then at 10 and 24 hours after the start of infusion on Days 1 and 8 of Cycles 1, 2 and 3 and at pre-infusion and 24 hours after the start of infusion on Days 1 and 8 of Cycles beyond Cycle 3 (time window at each sample collected: ±30 min).

[5] Tumor assessments should be performed at baseline and at the end of Cycle 3 (at C4D1/EOT visit). Any additional assessment can be arranged when clinically indicated.

[6] Hematology: Hemoglobin, Hematocrit, MCV, MCHC, MCH, RBC count, WBC count, WBC Differential, Absolute neutrophil count and Platelet count

Coagulation: PT, and INR

Chemistry: Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma-glutamyl transferase (GGT), Albumin, Total Protein, Creatinine, Urea (BUN), Uric acid, Total Creatinine Kinase (Ck) (if total Ck is above the ULN for the laboratory, Troponin-T or Troponin-I will be determined), Sodium, Potassium, Calcium, Chloride, Glucose, Triglycerides (TG) and Amylase.

The following lab panel will only be assessed at Screening Visit and EOT/Early Termination Visit: Creatinine Clearance, Total Cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL) and Lipase.

The following lab panel will only be assessed at Screening Visit: Hepatitis B/C

[7] Urinalysis: pH, Appearance, Color, Specific gravity, Viscosity, Turbidity, Ketones, Bilirubin, Blood, Glucose, Protein, Nitrites, Urobilinogen, Leukocyte esterases, Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC, and WBC.

[8] Hematology, clinical chemistry and urinalysis test results within 2 days prior to Cycle 1, Day 1 (C1D1) are acceptable. Only items not performed or obtained within 2 days prior to C1D1 should be tested.

[9] PK will only be performed on subjects enrolled in Stage I. PK blood samples will be taken immediately pre-infusion then at 24, 25, 26, 28 and 32 hours after the start of infusion on Days 1 and 8 of Cycle 3 if dose level of Cycle 3 is 24mg/m^2 (time window at each sample collected: ±5 min).

[10] Serum pregnancy test for women of childbearing potential must be performed ≤ 14 day prior to first dose.

[11] i.v. infusion for 24-hour of SCB01A on Days 1 and 8 of each cycle in a 3-week cycle (time window: 24 hours ±10 min).

[12] To be performed for all subjects at baseline and then during the trial only if grade 2 or above neurological symptoms experienced by the subject after receiving treatment with SCB01A.Refer Section 5.9 for further details.

[13] To be performed when necessary at the subject's request or per Investigator decision.

Table 2: Study Schedule, Additional Treatment Cycles/Visits

Study Visit[1]	Cycle 4			Cycle 5			Additional Cycles			EOT[2]	Early Withdrawal	Unscheduled
	C4D1	C4D8	C4D15*	C5D1	C5D8	C5D15*	CxD1	CxD8	CxD15*			
Study Days	64 (±1)	71 (±1)	78 (±2)	85 (±1)	92 (±1)	99 (±2)	NA	NA	NA	NA	NA	NA
Study Weeks	9	10	11	12	13	14	NA	NA	NA	NA	NA	NA
Activities												
Physical Examination	X	X		X	X		X	X		X	X	X
Vital Signs	X	X		X	X		X	X		X	X	X
BSA Calculation	X	X		X	X		X	X				
ECOG Performance Status	X	X		X	X		X	X		X	X	X
Adverse Events Review[3]	X	X		X	X		X	X		X	X	X
Concomitant Medication Review	X	X		X	X		X	X		X	X	X
12-Lead ECG	X[4]	X[4]		X[4]	X[4]		X[4]	X[4]		X	X	X [10]
Radiological Image Assessments[5]	X									X	X	X [10]
Laboratory Assessments[6]	X	X		X	X		X	X		X	X	X [10]
Urinalysis[7]	X			X			X			X	X	X [10]
Study Drug Administration [8]	X	X		X	X		X	X				
Nerve Conduction Velocity [9]												

***No Day 15 visit starting from Cycle 4**

[1] Subjects may continue treatment beyond 3 cycles (9 weeks) of SCB01A treatment per investigator discretion if they are experiencing clinical benefit, until the study is terminated. Refer to Table 2 for the schedule of assessments for additional treatment cycles.

[2] EOT visit should be conducted 14 or 21 days (±2 days) after last infusion, depending on last infusion was given on Day 8 or Day 1, respectively. Early withdrawal visit should be conducted after the subject received the last dose of study treatment. A toxicity follow-up (can be done by phone contact) should be performed 28±3 days after the last dose of study treatment.

[3] All AEs including SAEs must be reported from the time of start of study treatment and must continue to be followed for 28 days after last administration of study treatment.

[4] ECG will be performed prior to study drug administration (pre-infusion, 0 hr), and then at the end of the infusion (24 hr) on Days 1 and 8 of additional treatment cycles beyond Cycle 3 (time window at each sample collected: ±30 min).

[5] Tumor assessments will be assessed by using computerized tomography (CT) or MRI scans according to RECIST v1.1 at baseline, end of the first 3 cycles, and every three cycles thereafter until progression of disease (i.e. at or within 4 days prior to Day 1 of Cycle 4, 7, 10 and so on). For subjects who meet objective response criteria after the first 3 cycles of study treatment, confirmative radiological tumor assessments will be performed at least 4 weeks later.

[6] Hematology: Hemoglobin, Hematocrit, MCV, MCHC, MCH, RBC count, WBC count, WBC Differential, Absolute neutrophil count and Platelet count

Coagulation: PT, and INR

Chemistry: Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma-glutamyl transferase (GGT), Albumin, Total Protein, Creatinine, Urea (BUN), Uric acid, Total Creatinine Kinase (Ck) (if total Ck is above the ULN for the laboratory, Troponin-T or Troponin-I will be determined), Sodium, Potassium, Calcium, Chloride, Glucose, Triglycerides (TG) and Amylase.

The following lab panel will only be assessed at Screening Visit and EOT/Early Termination Visit: Creatinine Clearance, Total Cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and Lipase.

[7] Urinalysis: pH, Appearance, Color, Specific gravity, Viscosity, Turbidity, Ketones, Bilirubin, Blood, Glucose, Protein, Nitrites, Urobilinogen, Leukocyte esterases, Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC, and WBC.

[8] i.v. infusion for 24-hour of SCB01A on Days 1 and 8 of each cycle in a 3-week cycle (time window: 24 hours ±10 min).

[9] To be performed for all subjects at baseline and then during the trial only if grade 2 or above neurological symptoms experienced by the subject after receiving treatment with SCB01A.Refer Section 5.9 for further details.

[10] To be performed when necessary at the subject's request or per Investigator decision.

Table 3: Study Schedule, Follow-Up Phase

Study Visit [1]	FU1	FU2	FU3	FU4	FU5	FUx [2]	Unscheduled
Study Days*	**85 (±3)**	**106 (±3)**	**127 (±3)**	**190 (±7)**	**253 (±7)**	**NA**	**NA**
Study Weeks*	**12**	**15**	**18**	**27**	**36**	**NA**	**NA**
Activities							
Survival Status [3]	X	X	X	X	X	X	X
Cancer Therapy [4]	X	X	X	X	X	X	X

*This reflects the time points for subjects who didn't receive additional treatment cycles beyond Cycle 3. For subjects who undergo addition treatment cycles the follow-up visits will be conducted after discontinuation of treatment at every 3 weeks during the first 9 weeks, thereafter every 9 weeks until the end of the study.

[1] Follow-up visits will be performed after the subject completes EOT visit or early withdrawal visit. Follow-up visits will be scheduled every 3 weeks for 9 weeks, thereafter every 9 weeks until the end of the study. These visits can be conducted by phone.

[2] Additional follow-up visits every 9 weeks until the end of the study.

[3] Follow-up for survival status will performed via telephone call if the site is unable to confirm via chart review or clinical visit.

[4] Cancer therapies evaluated at the Follow-Up visit or phone call include anti-cancer medications, cancer-related radiotherapy, and cancer-related surgery/procedures since last contact.

1. Introduction

1.1. Background

Vascular disrupting agents (VDAs) are designed to disrupt the already abnormal vasculature that supports tumors by targeting their already dysmorphic endothelial cells. VDAs induce rapid and selective shutdown of the tumor blood supply resulting in tumor death while leaving the blood supply in normal tissues relatively intact[2,3]. The largest group of VDAs is the tubulin-binding combretastatins. Combretastatin A4 phosphate (CA4P) is a small organic molecule found in the bark of the African bush willow tree (*Combretum caffrum)*[2]. Endothelial cells have been shown to be particularly sensitive to the effects of CA4P compared with various other cell types and several preclinical studies have demonstrated selective *in vitro* activity of CA4P against proliferating endothelial cells2.

SCB01A is a novel heterocyclic combretastatin A-4 (CA-4) analogue that binds to the colchicines-binding site of the ß-subunit of tubulin thereby inhibiting polymerization and effectively preventing mitosis in a manner similar to that seen with other "spindle poisons", e.g., vincristine, vinblastine and vinorelbine, which are in use as cancer chemotherapeutic agents. Because SCB01A has VDAs property, SynCore plans to develop SCB01A as a treatment for a variety of oncologic indications such as non-small cell lung cancer, breast cancer, head and neck cancer, acute lymphoblastic leukemia, nephroblastoma and testicular cancer.

Compounds that interfere with the cell cycle by interfering with normal biology of tubulin are prominent anti-cancer agents because they can inhibit the proliferation of tumor cell lines derived from various organs. Tubulin-containing structures are important for diverse cellular functions, including chromosome segregation during cell division, intracellular transport, development, and maintenance of cell shape, cell motility, and possibly distribution of molecules on cell membranes. The drugs that interact with tubulin are heterogeneous in chemical structure. However, a common characteristic of these agents is that while binding to tubulin, they cause its precipitation and sequestration to interrupt many important biologic functions that depend on the microtubular class of subcellular organelles. One class of well-characterized and clinically used antimitotic drugs is those of natural origin, including the taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine, vinorelbine), and podophyllotoxins. These agents either inhibit the polymerization of tubulin (vinca alkaloids) or prevent the disassembly of microtubules (taxanes).

SCB01A has been studied extensively since 2005 to evaluate its pharmacokinetic (PK) profile, metabolism, *in vitro* genotoxicity, and acute and sub-acute toxicity. SCB01A binds to colchicine binding sites of tubulin much more strongly than colchicines, and as with other antimicrotubule inhibitors, it arrests the cells on the G2/M phase in a time- and concentration-dependent manner, subsequently leading to cell apoptosis. Additional studies indicate that the effect of SCB01A on cell-cycle arrest is associated with an increase in cyclin B1 levels and a mobility shift of Cdc2 and Cdc25C. The changes in Cdc2 and Cdc25C coincide with the appearance of phosphoepitopes

recognized by a marker of mitosis, MPM-2. Furthermore, phosphorylated forms of Bcl-2, perturbed membrane mitochondrial potential, and activation of the caspase 3 cascade may be involved in SCB01A-induced apoptosis.

1.2. Rationale for the Study

The research data available to date indicate that SCB01A is a promising anti-cancer agent with vascular disrupting activity that has potential for treatment of various malignancies, particularly for patients with drug resistance to existing therapies. The drug has been trialed in human subjects in dose-escalation phase I study, and maximum tolerated dose (MTD) is 24 mg/m^2 (each cycle consists of one intravenous [i.v.] administration of SCB01A via a central line every 3 weeks). In the phase I study, partial response (PR) (shrinkage of tumor size to 50%) was observed in cycle 9 (3 mg/m^2) of one subject with right buccal squamous cell carcinoma and disease stabilization lasted for 14 cycles. Summary from current clinical findings note a total of 19/33 (57.6%) subjects had stable disease (SD) for at least 2 cycles. Extended disease stabilizations were especially observed for 23 cycles in one subject with cholangiocarcinoma (4 mg/m^2) and 15 cycles in one subject with rectal cancer (3 mg/m^2) respectively, suggested that the most prominent SD subjects remain in low dose (less than 6.5 mg/m^2).

Pre-clinical study of SCB01A showed that the concentrations at which tubulin inhibition occurred were around 80 nM for 24-hour exposure or 200 nM for 6-hour exposure. However, pharmacokinetic (PK) results of both phase I study and an ongoing phase II study showed that the average elimination half-life (t1/2) of a 3-hours i.v. infusion of SCB01A is approximately 2.5 hours and almost no SCB01A can be detected after 10 hours, indicating most subjects were treated in short API exposure time and may have been insufficient to achieve efficacy. Furthermore, clinical experiences demonstrated that extended infusion duration may reduce susceptible chemotherapy induced adverse reaction especially peripheral neuropathy (JCO 1999, 17(11): 3403-11). Summary from both efficacy and safety evidences suggesting that to extend the cumulative exposure duration of SCB01A beyond effective concentration in blood may be benefit to patient's best interest.

Two phase I clinical studies were performed "A Phase 1 Dose Escalation Study of SCB01A in Subjects with Advanced Solid Tumors Who Have Failed Standard Therapy" and "Long-Term Compassionate Use Study for Continued Administration of SCB01A in Subjects Who Completed Treatment With SCB01A in the Previous Protocol #SCB01A-01" respectively. The phase I study demonstrated that SCB01A has encouraging safety and efficacy and support for further Phase II study. 33 subjects were enrolled in the study and 31 subjects completed the main treatment. Among the 31 subjects, 11 of them completed the extension treatment of SCB01A. Up to date, 5 subjects, two in main and extension period respectively, experienced 7 SUSAR events. (Including gastric ulcer bleeding, thrombocytopenia, cough, radiation recall dermatitis, thromboembolic event, muscle weakness lower limb, and sepsis). In addition, 5 dose limiting toxicities and 61 adverse reactions were reported in this study.

The aim of this Phase II study with SCB01A is to determine the efficacy and safety of SCB01A in subjects with squamous cell carcinoma of head and neck who have failed previous platinum based therapies.

2. Study Objectives

This is a Phase II study with intra-subject dose escalation to evaluate the efficacy and safety of SCB01A in subjects with recurrent or metastatic squamous cell carcinoma in head and neck.

2.1. Primary Objective

To assess the objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

2.2. Secondary Objective

The secondary objectives of the study are listed below:

- To evaluate the safety and toxicity profile of SCB01A.
- To assess the overall survival (OS) after first treatment with SCB01A.
- To assess the progression-free survival (PFS).
- To assess the best overall tumor response after treatment with SCB01A.
- To assess the PK profile.

3. Investigational Plan

3.1. Description of Overall Study Design and Plan

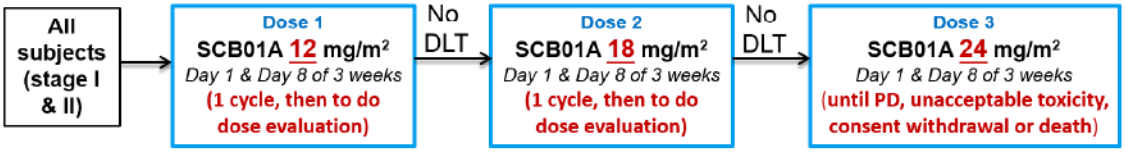
This study is a multicenter, open-label, Phase II trial. The study will be conducted in two stages:

- **Stage I**: A total of up to 10 evaluable subjects will be enrolled for Stage I to receive at least 3 cycles of i.v. administration by 24-hours infusion of SCB01A under intra-subject dose escalation regimen. The tumor response review will be performed with the subjects who completed at least 3 cycles of SCB01A treatment. If at least one response (CR or PR) is observed, another 19 evaluable subjects will be enrolled into Stage II.
- **Stage II**: 19 evaluable subjects will be enrolled at stage II and treated with the same intra-subject dose escalation regimen from starting dose 12 mg/m^2. The tumor response review will be performed with the subjects who completed 3 cycles of SCB01A treatment.

Intra-Subject Dose Escalation

All subjects enrolled in this study will be treated from the same starting dose 12 mg/m^2 (Dose 1) given on Days 1 and 8 in a 21-day cycle by 24 h IV infusion. If the subject experiences no dose-limiting toxicity (DLT) during the period, dose escalation of SCB01A to 18 mg/m^2 (Dose 2) occurred from cycle 2; and increased to 24 mg/m^2 (Dose 3) on cycle 3 (Figure 1).

Figure 1: Intra-Subject Dose Escalation Plan



Dose Modification

If the subject experiences a DLT at a given dose level, dose escalation will be halted and a reduced dose will be given to the subject. Dose adjustments were allowed based on the toxicity, efficacy evaluation, and clinical judgment by physician.

Rules for dose modifications of the study (Figure 2) are listed as following:

1. Dose 1 (12 mg/m^2), will be the starting dose regimen for all subjects. Safety and clinical benefit observation will be performed prior to drug administration on Cycle 2 Day 1.
    a) Dose de-escalation: if any DLT experienced before Cycle 1 Day 8, the dose will be de-escalated to Dose 1a (9 mg/m^2) for Cycle 1 Day 8. If first DLT during Cycle 1 is experienced after Cycle 1 Day 8, the dose will be de-escalated to Dose 1a (9 mg/m2) for Cycle 2. If no DLT is observed in Dose 1a, the subjects will receive the Dose 1a until PD, consent withdraw or death.

Once more dose de-escalation (Dose 1b, 7 mg/m^2) will be allowed if another DLT is observed in Dose 1a.

b) Dose maintained: If clinical benefit observed at Dose 1 and without DLT, the dose level can be maintained until PD, intolerable toxicity, consent withdraw or death.

2. Dose 2 (18 mg/m^2), will be administrated for one cycle and safety and clinical benefit observation will be performed prior to drug administration on Cycle 3 Day 1.

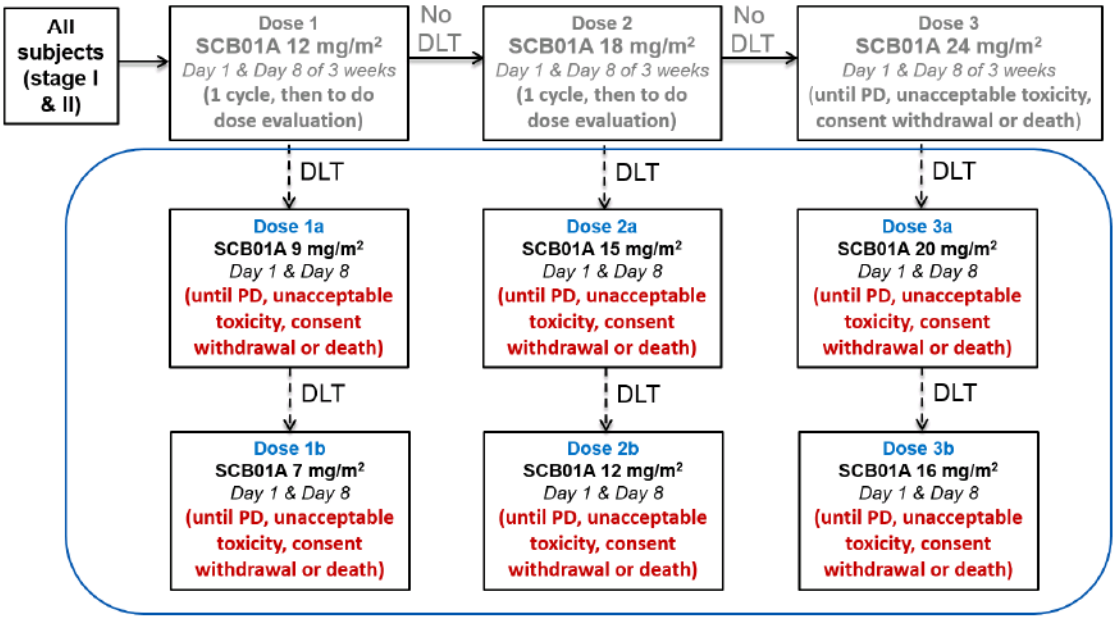
   a) Dose de-escalation: if any DLT experienced before Cycle 2 Day 8, the dose will be de-escalated to Dose 2a (15 mg/m^2) for Cycle 2 Day 8. If first DLT during Cycle 2 is experienced after Cycle 2 Day 8, the dose will be de-escalated to Dose 2a (15 mg/m^2) for Cycle 3. If no DLT is observed in Dose 2a, the subjects will receive the Dose 2a until PD, consent withdraw or death. Once more dose de-escalation (Dose 2b, 12 mg/m^2) will be allowed if another DLT is observed in Dose 2a.

   b) Dose maintained: If clinical benefit observed at Dose 2 and without DLT, the Dose 2 can be continued until PD, intolerable toxicity, consent withdraw or death.

3. Dose 3 (24 mg/m^2), will be administrated for one cycle and safety and tumor assessment will be performed prior to drug administration on Cycle 4 Day 1.

   a) Dose de-escalation: if any DLT experienced before Cycle 3 Day 8, the dose will be de-escalated to Dose 3a (20 mg/m^2) for Cycle 3 Day 8. If first DLT during Cycle 3 is experienced after Cycle 3 Day 8, the dose will be de-escalated to Dose 3a (20 mg/m^2) for Cycle 3. If no DLT is observed in Dose 3a, the subjects will receive the Dose 3a until PD, consent withdraw or death. Once more dose de-escalation (Dose 3b, 16 mg/m^2) will be allowed if another DLT is observed in Dose 3a.

Figure 2: Dose Modification



If the subject experienced any neurotoxic DLT, the subject will be withdrawn.

Subjects will be considered to be non-evaluable for ORR if they receive study drug for fewer than 9 weeks (3 cycles) of treatment for any reason other than study-drug related toxicity. Non-evaluable subjects will be replaced.

All subjects will be treated until the occurrence of progressive disease, intolerable adverse events (AEs)/toxicity, consent withdrawal or death. After discontinuation of study treatment, all subjects will be followed for survival and disease-specific therapies of the clinician's choice will be administered. Follow-up visits will be scheduled every 3 weeks for 9 weeks (i.e. week 3, week 6, and week 9), thereafter every 9 weeks until the end of the study.

End of study will be either 12 months after the 1st treatment with SCB01A or end of 27 weeks survival follow-up, whichever comes later.

Data and Safety Monitoring Board (DSMB)

The responsibilities of the DSMB, composed of medical monitors (physicians experienced in oncology studies) and at least one statistician, are to review and evaluate the data for safety, study conduct and progress, and make recommendations concerning the continuation, modification, or termination of study. Serial assessments of PK results also may be taken into account for safety evaluation. A neurologist will be invited to join DSMB meeting as a consultant when neurotoxicity occurred.

The document review or meeting of DSMB will be held when the following scenarios:

- A subject is not recovered from Grade 2 neurotoxicity over three weeks;
- A subject revealed Grade 3 or above neurotoxicity;
- After 10 evaluable subjects finished the study in Stage I;

The schedule of assessments is shown in detail in Table 1, Table 2 and Table 3. The results of protocol specific assessments and procedures will be recorded in the source documents for the subjects and on the appropriate page of the case report form (CRF). The different study days are described below.

3.2. Screening and Treatment Phase

3.2.1. Screening Evaluations

The following procedures/assessments will be performed during the screening visit, which will be performed within 28 days prior to Day 1 of Cycle 1:

- Written informed consent
- Initial history and pre-existing conditions (including all prior anti-tumoral therapy, surgery or radiotherapy related to Head and Neck cancer)
- Review of inclusion and exclusion criteria
- Physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) performance status
- Concomitant medication
- 12-lead ECG
- Radiological imaging according to RECIST v1.1
- Laboratory tests (hematology, clinical chemistry, coagulation and serum pregnancy test)
- Urinalysis
- Nerve Conduction Velocity

3.2.2. Cycle 1, Day 1 (C1D1)

The following procedures/assessments will be performed:

Pre-treatment

- Record pre-existing conditions (baseline signs and symptoms with an onset between time of signing the informed consent and the first dose of study drug)
- Physical examination
- Vital signs
- Calculation of body surface area (BSA)
- ECOG performance status
- Concomitant medication
- 12-lead ECG
- Laboratory tests (hematology*, clinical chemistry* and coagulation)
- Urinalysis*

*Test results within 2 days are acceptable, only items not performed for screening within 2 days before this visit need to be tested again.

Study Drug Administration

- Study treatment - i.v. infusion for 24-hour of SCB01A

Post-initiation of Study Drug Administration

- Vital signs
- AEs
- Concomitant medication
- 12-lead ECG - *At 10 and 24 hours after the start of infusion*

3.2.3. Cycle 1, Day 8 (C1D8) ±1 day

The following assessments will be performed:

- Physical examination
- Vital signs
- Calculation of BSA
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG - *At pre-infusion, 10 and 24 hours after the start of infusion*
- Laboratory tests (hematology, clinical chemistry and coagulation)
- Study treatment infusion

3.2.4. Cycle 1, Day 15 (C1D15) ±2 days

The following assessments will be performed:

- Physical examination
- Vital signs
- ECOG performance status
- AEs
- Concomitant medication
- Laboratory tests (hematology, clinical chemistry and coagulation)

3.2.5. Cycle 2, Day 1 (C2D1) ±1 day

The following assessments will be performed:

- Physical examination
- Vital signs

- Calculation of BSA
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG - *At pre-infusion, 10 and 24 hours after the start of infusion*
- Laboratory tests (hematology, clinical chemistry and coagulation)
- Urinalysis
- Study treatment infusion

3.2.6. Cycle 2, Day 8 (C2D8) ±1 day

The assessments on Day 8 of Cycle 2 is identical to Cycle 1, Day 8 (see Section 3.2.3)

3.2.7. Cycle 2, Day 15 (C2D15) ±2 days

The assessments on Day 15 of Cycle 2 is identical to Cycle 1, Day 15 (see Section 3.2.4)

3.2.8. Cycle 3, Day 1 (C3D1) ±1 day

The assessments on Day 1 of Cycle 3 are identical to Cycle 2, Day 1 (see Section 3.2.5) with the exception of extra PK sampling if dose level of Cycle 3 is 24mg/m^2 - At pre-infusion, 24, 25, 26, 28, and 32 hours after the start of infusion.

3.2.9. Cycle 3, Day 8 (C3D8) ±1 day

The assessments on Day 8 of Cycle 3 is identical to Cycle 1, Day 8 and Cycle 2, Day 8 (see Section 3.2.3 and 3.2.6) with the exception of extra PK sampling if dose level of Cycle 3 is 24mg/m^2 - At pre-infusion, 24, 25, 26, 28, and 32 hours after the start of infusion.

3.2.10. Cycle 3, Day 15 (C3D15) ±2 days

The assessments on Day 15 of Cycle 3 are identical to Cycle 1, Day 15 and Cycle 2, Day 15 (see Section 3.2.4 and 3.2.7).

3.2.11. Cycle 4, Days 1 and 8 (C4D1 and C4D8)

If the subject, per the investigator's discretion, is experiencing clinical benefit, they may continue with treatment of SCB01A at the same dose until the study is terminated. The assessments on Days 1 and 8 will continue to be the same as for Cycle 2, Day 1 and Day 8 (see Section 3.2.5 and 3.2.6, respectively) with the exception that ECG will only be performed prior to study drug administration (pre-infusion, 0 hr), and then at the end of the infusion (24 hr) on Days 1 and 8 of additional treatment cycles beyond Cycle 3.

Tumor assessment should be performed at baseline, and at the end of every 3 cycles which needs to be arranged within 4 days prior to the next cycle.

Note: No Day 15 visit starting from Cycle 4.

3.3. End of Treatment (EOT) Evaluation/Early Withdrawal

EOT visit should be conducted 14 or 21 days (±2 days) after last infusion, depending on last infusion was given on Day 8 or Day 1, respectively. Early withdrawal visit should be conducted after the subject receives the last dose of study treatment.

The following assessments will be performed at the EOT/early withdrawal visit:

- Physical examination
- Vital signs
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG
- Tumor assessment (radiological imaging)
- Laboratory tests (hematology, clinical chemistry and coagulation)
- Urinalysis

3.4. Follow-up

After discontinuation of study treatment, all subjects will be followed for survival and disease-specific therapies of the clinician's choice will be administered. The data will be collected and can be done by telephone. Follow-up visits will be scheduled every 3 weeks for 9 weeks, thereafter every 9 weeks until the end of the study.

3.5. Unscheduled Visit

The following assessments will be performed during an unscheduled visit:

- Physical examination
- Vital signs
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG*

- Tumor assessment (radiological imaging)*
- Laboratory tests* (hematology, clinical chemistry and coagulation)
- Urinalysis*

*To be performed when necessary at the subject's request or per Investigator decision.

3.6. Study Design, Including the Choice of Control Groups

There is no control group in this Phase II study. The rationale for the study is discussed in Section 1.2.

3.7. Selection of Study Population

3.7.1. Inclusion Criteria

1. Aged ≥20 years;
2. Signed informed consent obtained prior to initiation of any study-specific procedures and treatment;
3. Histological or cytological confirmed squamous cell carcinoma of head and neck, excluding nasopharyngeal carcinoma;
4. Subjects with unresectable, unfeasible radiotherapy, recurrent or metastatic head and neck squamous cell carcinoma, after previous treatment with platinum agent;
5. Subjects must have at least one measurable tumor lesion as defined by RECIST version 1.1 as assessed by the investigator (local radiological image assessment) or clinically evaluable disease. Physical and neurological examinations, and radiographic studies have to be performed within 28 days of Cycle 1 Day 1;
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1;
7. Life expectancy of 12 weeks or longer;
8. Concurrent local therapy is not allowed, but concurrent palliative radiation therapy to non-measurable sites of disease such as painful bone metastasis is permitted;
9. All eligible subjects of childbearing potential have to use effective contraception; that is, double barrier contraceptive methods;
10. Documented progressive disease within past 6 months;
11. Adequate bone marrow reserve, cardiac, renal and liver function:
    a. Absolute neutrophil count (ANC) > 1.5 x 10^9/L;
    b. White blood cell (WBC) > 3 x 10^9/L
    c. Platelet count > 75 x 10^9/L;
    d. Hemoglobin > 9 g/dL (> 5.6 mmol/l);

e. Prothrombin time (PT)/international normalized ratio (INR) ≤1.5 x upper limit of normal (ULN)

f. Creatinine clearance (Cockcroft & Gault formula) >50 mL/min;

g. Alanine aminotransferase (ALT, SGPT) and aspartate aminotransferase (AST, SGOT) and Alkaline Phosphatase (ALP) < 3 x ULN; AST/ALT ≦ 5 x ULN if liver metastasis

h. Serum albumin ≥ 3 g/dL;

i. Total Bilirubin ≤ 1.5 x ULN

j. QTc < 450 msec

3.7.2. Exclusion Criteria:

1. Known primary CNS malignancy or CNS involvement (except for brain metastases that have been treated and are stable and subject is off steroids);
2. Chemotherapy, radiation therapy, major surgery or investigational agents including immune or target therapies less than 4 weeks prior to study drug treatment;
3. History of malignancy other than head and neck cancer with the exception of early stage non-melanoma skin cancer or carcinoma *in situ* of cervix;
4. History of liver cirrhosis;
5. Active hepatitis B or hepatitis C infection
6. Clinical significant pulmonary obstructive or clinical significant pulmonary restrictive diseases (grade >2);
7. Clinically significant cardiac disease (NYHA class > 2);
8. Other serious illness or medial conditions, such as active infection, unresolved bowel obstruction, or psychiatric disorders;
9. Known HIV positivity;
10. Pregnant or breast-feeding subjects, and men and women of child-bearing potential not using effective contraception while on study treatment;

− For females of child bearing potential (without using hormonal contraceptives for at least 2 months prior to start of screening) a double contraception method is required during the entire study meeting the criteria for an effective method of birth control, i.e. at least two effective birth control methods* (1 of which must be a barrier method) such as condoms, diaphragms or intra-uterine devices must be used.
* Acceptable forms include:
Consistent and correct usage of established oral contraception.
Established intrauterine device or intrauterine system.
Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
− Male participants with partners of child bearing potential are required to use barrier contraception in addition to having their partner use another method of contraception during the trial and for 3 months after the last dose. Male participants will also be advised to abstain from sexual intercourse with pregnant or lactating women, or to use condoms.

11. Known hypersensitivity to any component of SCB01A or excipients including Solutol®, alcohol, and PEG300;
12. History of exposure to SCB01A or its analogues;
13. History of active or significant neurological disorder or psychiatric disorder that would prohibit the understanding and giving of informed consent, or would interfere with the clinical and radiological evaluation of central nervous system during the trial;
14. Peripheral neuropathy (≥ grade 2);
15. Any other reason the investigator deems the subject to be unsuitable for the study.

3.8. Removal of Subjects from Treatment or Assessment

3.8.1. Early Discontinuation of the Study

The study may be discontinued at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of subjects.

The study may also be discontinued based on evidence of either substantial efficacy, or likely failure to meet the primary objective.

3.8.2. Early Discontinuation of Individual Subjects

The investigator may remove a subject from study treatment at his/her discretion for any of the following reasons:

- Disease progression
- Intolerable AE(s) or failure to tolerate the study treatment
- Subject decides to discontinue study therapy
- Any medically appropriate reason or significant protocol violation, in the opinion of the investigator
- Lost follow-up

Subjects may decide to discontinue study treatment for any reason. Subjects who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, subjects may elect to withdraw consent and decline further participation in the trial.

All subjects will be followed until disease progression, withdrawal of consent, intolerable AEs/toxicity, death, loss to follow-up or the end of the study.

The investigator must determine the primary reason for a subject's discontinuation of study treatment and record this information on the CRF. Subjects who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

4. Treatments

4.1. Identity of Investigational Product (IP)

SCB01A (a novel heterocyclic CA-4 analogue) is dissolved in absolute EtOH, PEG 300, and Solutol®. Solutol® (Macrogol 15 Hydroxystearate) is a non-ionic solubilizer for injection solutions and conforms to the requirements of the European Pharmacopoeia monograph. PEG 300 (Macrogol 300) is a mixture of polymers of ethylene oxide and water and their ethers. The average molecular weight is about 300 and conforms to the requirements of the European Pharmacopoeia monograph. Dehydrated alcohol contains > 99.2% by weight, corresponding to > 99.5% by volume at 15.56°C of C2H5OH and conforms to the requirements of the US Pharmacopoeia monograph.

SCB01A is a water insoluble, white to slightly yellow solid. At room temperature, the water solubility of SCB01A is 0.9 µg/ml. Formulated SCB01A is a sterile, clean, colorless to slightly yellow viscous solution.

4.2. Study Drug Packaging and Labeling

The study drug is packaged in glass vials with a rubber stopper and flip-off seal labeled with the study protocol number, contents, directions for use, storage directions, clinical trial statement, and sponsor name.

4.3. Study Drug Storage Conditions

Formulated SCB01A can be stored at temperatures 15-25 °C. Although direct data on its photosensitivity is unavailable, the avoidance of light is recommended.

4.4. Study Drug Dose Preparation and Administration

The study drug, SCB01A is packaged as 10 mg/ml in 5 ml/vial. The injection volume of SCB01A should be calculated based on the BSA of the subject. (See Section 5.3). The study drug will be diluted in normal saline solution before infusion. An equal volume of normal saline will be drawn out from a 250 ml normal saline container before adding the SCB01A injection solution. The total volume of study drug diluted solution will be equal to 250 ml. The study drug should be administered for 24 hours (time window 24 hours±10 mins) by i.v. infusion through a central line in order to avoid potential extravasation and tissue necrosis. The duration from drug dilution to completion of 24h i.v. infusion must not exceed a maximum of 28 hours. For further details, please refer to the IMP Manual.

4.5. Study Drug Accountability

Drug Accountability records will be maintained by the study sites. All used and partially used supplies of SCB01A will be destroyed by the study site in accordance with institutional policies after accountability performed by the monitor. The site will maintain detailed documentation of the number and identification of vials, which are

used and destroyed, and copies of these documents will be provided to the sponsor or Clinical Research Organization (CRO). Disposition of all unused study drug will be carried out according to instructions provided by the sponsor or CRO at the end of the study and after a final drug accountability assessment is performed by the monitor.

4.6. Method of Assigning Subjects to Treatment Groups

There is no randomization in this study. All subjects will receive the study drug, and the dose as per intra-subject dose escalation plan. Subjects will be assigned to Dose 1 (12 mg/m^2) initially on Days 1 and 8 of Cycle 1. If the subject experiences no DLT during this period, dose escalation of SCB01A to Dose level 2 (18 mg/m^2) occurred from Cycle 2; and increased to Dose level 3 (24 mg/m^2) on Cycle 3.

4.7. Selection of Doses in the Study

Doses were selected based on pre-clinical data and data obtained from Phase I and ongoing Phase II studies as described in Section 1.2.

4.8. Selection and Timing of Dose for each Subject

The selection and timing of dose for each subject is described in Section 3.1.

Subjects entered into Stage I and II will be allocated Dose 1, 2 and 3 under intra-subject dose escalation regimen. If the subject experiences a DLT at a given dose level, dose escalation will be halted and a reduced dose will be given to the subject. Dose adjustments were allowed based on the toxicity, efficacy evaluation, and clinical judgment by physician.

Dose 1: **One i.v. administration of 12 mg/m^2 SCB01A on Days 1 and 8 of a Cycle 1;**

Dose 1a: one i.v. administration of 9 mg/m^2 SCB01A
Dose de-escalation (if any DLT experienced during Dose 1)

Dose 1b: one i.v. administration of 7 mg/m^2 SCB01A
Dose de-escalation (if any DLT experienced during Dose 1a)

Dose 2: **One i.v. administration of 18 mg/m^2 SCB01A on Days 1 and 8 of a Cycle 2;**

Dose 2a: one i.v. administration of 15 mg/m^2 SCB01A
Dose de-escalation (if any DLT experienced during Dose 2)

Dose 2b: one i.v. administration of 12 mg/m^2 SCB01A
Dose de-escalation (if any DLT experienced during Dose 2a)

Dose 3: **One i.v. administration of 24 mg/m^2 SCB01A on Days 1 and 8 of a Cycle 3;**

Dose 3a: one i.v. administration of 20 mg/m^2 SCB01A
Dose de-escalation (if any DLT experienced during Dose 3)

Dose 3b: one i.v. administration of 16 mg/m^2 SCB01A
Dose de-escalation (if any DLT experienced during Dose 3a)

4.9. Dose Adjustment and Toxicity Management

If a study treatment-related Grade 3 or 4 AE occurs, the study treatment will be placed on hold until the event is resolved to Grade ≤ 1 or returns to baseline before resuming the study drug. If the Grade 3 or 4 event does not resolve or return to baseline within 14 days or return to Grade 3 or 4 toxicity after resuming, treatment with the study drug will cease. However the subject should be followed-up for survival analysis until the end of the study.

4.10. Blinding

This is an open-labeled study. Therefore blinding procedures are not applicable.

4.11. Prior and Concomitant Therapy

Concomitant medications are defined as any prescription or over-the-counter medications, including vitamins, dietary supplements, and oral herbal medications.

All medications that are taken by, or being administered to, the subject at the time of the Screening Visit, within 30 days prior to the Screening Visit, till the end of treatment (EOT) will be recorded in the CRF.

For each medication the following will be documented:

- Medication/treatment name (generic name).
- Dose, unit, and frequency of dosing (total daily dose).
- Route of administration
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing)

4.12. Prohibited Medications

Subjects are prohibited from using any of the following medications during study:

1. Any investigational drug, chemotherapy, targeting agent(s), biology therapy, immunotherapy, herbal medicine or hormonal therapy administered within 4 weeks before the date of the first study treatment should be excluded from enrolment until at least 4 weeks have passed.
2. Concomitant administrations of compounds that inhibit CYP1A2 or CYP2D6 are prohibited for 3 weeks prior to study drug infusions and throughout the study. Excluded concomitant medications of CYP1A2 and CYP2D6 inhibitors include (except antibiotics whenever they are clinically indicated): fluvoxamine, ciprofloxacin, cimetidine, bupropion, cinacalcet, fluoxetine, paroxetine, quinidine1, duloxetine, sertraline, terbinafine and amiodarone.

   Note: 1. 5-HT_3 antagonist (serotonin antagonist) with the antiemetic effect can be used as a substitute for metoclopramide in preventing nausea and vomiting activity. 2. Steroid can be used as a substitute for diphenhydramine in treating allergies.

3. Therapy with anticoagulants, antiplatelet treatments (e.g. Warfarin, heparins) are not allowed during the study.

4.13. Treatment Compliance

Subjects will be infused with their study treatment at the clinical site by trained personnel and the infusion start and end times will be recorded in source documents and in the CRF.

5. Study Assessments and Procedures

5.1. Medical History

Medical history will be assessed at screening and will include the following:

1. Histological or cytological confirmed metastatic squamous cell carcinoma in head and neck.
2. At least one measurable tumor lesion according to RECIST version 1.1 as assessed by the investigator (local radiological image assessment).
3. Details of the prior therapy that failed or intolerable to platinum agent and also not amenable to further surgical or radiation therapy due to disease progression or toxicity.
4. Smoking status (current smoker or past history of smoking).
5. Betel nut consumption status or history.
6. Additionally, all relevant medical histories, medical conditions, or symptoms experienced during 30 days prior to screening are to be recorded, using the body system categories outlined below. For each history, the specific medical terminology for the disease/disorder/condition, the date of diagnosis, and the history status (resolved or ongoing) will be documented. Surgery and procedure: within 1 year prior to screening visit should be recorded, cancer history should be recorded on life time base.

5.2. Physical Examination

A complete physical examination will be performed at baseline and each clinic visit prior to drug administration, if applicable and the EOT/Early Withdrawal visit to include a review of all systems. Each body system will be classified as being either normal or abnormal, with abnormalities for each body system noted. Subsequent physical examinations will identify changes from the baseline examination with both positive and negative changes being noted. The physical examination will include routine examinations for the following:

- Abnormalities of the extremities
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- Neurologic abnormalities

Any other body system, for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the participant or could impact safety or efficacy results for the study subject; i.e., the abnormality is clinically significant.

5.3. BSA Calculation

BSA will be calculated on dosing days, using the formula below[4]:

$$BSA\ (m^2) = [Height\ (cm) \times Body\ Weight\ (kg)/3600]^{½}$$

The total dose (mg) will be calculated as:

$$Total\ Dose\ (mg) = Dose\ Level\ (mg/m^2) \times BSA\ (m^2)$$

5.4. Vital Signs

Vital signs will be obtained at screening/baseline, at all clinic visits during treatment phase and at the EOT/Early Withdrawal visit.

Note: *On days of study treatment administration (Day 1 and 8), the Vitals will be taken two times (pre- and post-treatment). Post-Treatment Vital Signs will be assessed at the end of 24-hour study treatment infusion.*

Vital signs will include height, weight, heart rate, blood pressure, respiratory rate, and body temperature. Respiratory rate, heart rate, and blood pressure (systolic/diastolic) will be obtained after the subject has been at rest for at least 5 minutes in a sitting position. Height (cm) measurement will only be performed at baseline and weight (kg) measurement will be performed at each visit before a study treatment infusion.

If vital sign measurements coincide with a blood sample, the vital signs will be taken prior to obtaining the blood sample.

Body temperature will be taken and recorded in degrees Centigrade.

5.5. ECOG Performance Status

The ECOG performance status will be documented at baseline and at all clinic visits.

Table 4: ECOG Performance Status Scale[5]

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

5.6. 12-lead ECG

During Stage I and II, the 12-lead EGC will be obtained at Screening Visit, prior to study drug administration, and then at 10 and 24 hours after the start of infusion on Days 1 and 8 of Cycles 1, 2 and 3 and at EOT/Early Withdrawal visit.

For subjects who are continuing treatment beyond 3 cycles (9 weeks), the ECG will be obtained at every treatment cycle prior to study drug administration (0 hr) and at the end of the study drug administration (24 hr).

The allowed time window for each ECG assessment is ±30 min. ECGs will be obtained whenever deemed necessary at the investigator's discretion. The following ECG measurements will be recorded in the subject's source documents and on the appropriate page(s) of the CRF:

- PR interval
- QRS interval
- QTc interval
- Investigator's interpretation of the ECG results (NOTE: for all abnormalities, the nature of the abnormality will be noted and the Investigator will comment regarding the clinical significance of the abnormality).

5.7. Laboratory Assessments

The local laboratory for the study site will be used and all procedures will be performed following the standard operating procedure (SOP) of the local laboratory.

Hematology, clinical chemistry and Coagulation blood samples will be obtained at screening, all clinic visits and the EOT/Early Withdrawal visit. The number of sample collection will differ based on actual number of cycles completed and if there are any unscheduled visits done.

Urinalysis will be determined at Screening and Day 1 of each cycle prior to study treatment administration.

The parameters assessed are detailed below:

<u>Hematology</u>

Hemoglobin, Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), RBC count, WBC count, WBC Differential, Absolute neutrophil count and Platelet count

<u>Clinical Chemistry</u>

Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma-glutamyl transferase (GGT), Albumin, Total Protein, Creatinine, Urea (BUN), Uric acid, Total Creatinine Kinase (Ck) (if total Ck is above the ULN for the laboratory, Troponin-T or Troponin-I will be determined), Sodium, Potassium, Calcium, Chloride, Glucose, Triglycerides (TG) and Amylase.

The following lab panel will only be assessed at Screening Visit and EOT/early termination visit: Creatinine Clearance, Total Cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL) and Lipase.

Coagulation

PT, INR

Urinalysis

pH, Appearance, Color, Specific gravity, Viscosity, Turbidity, Ketones, Bilirubin, Blood, Glucose, Protein, Nitrites, Urobilinogen, Leukocyte esterases, Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC, and WBC.

Pregnancy test

A serum beta-HCG test for women of childbearing potential will be performed ≤ 14 days prior to the first dose of study treatment.

5.8. PK Assessments

PK Procedures

PK will only be performed on subjects enrolled in Stage I. PK blood samples will be taken immediately pre-infusion then at 24, 25, 26, 28, and 32 hours after the start of infusion on Days 1 and 8 of Cycle 3 if dose level of Cycle 3 is 24mg/m^2 (time window at each sample collected: ±5 min). Twelve (12) samples (5 mL) will be taken (60 mL in total). Also see Section 6.4 for more detail.

5.9. Nerve Conduction Velocity

Subjects will undergo testing for the nerve conduction velocity at the following time points based on neurological symptoms:

a. Baseline: within 28 days before C1D1 for all subjects.

b. Within 7-30 days, since the onset for Grade 2 or above neurological symptom after receiving treatment of SCB01A; per investigator's decision, an optional NCV test can be performed within 7 days.

c. Within 90-120 days, since the consent withdraw or received the last treatment of SCB01A, after the onset for Grade 2 or above neurological symptom after receiving treatment of SCB01A;

The test results of nerve conduction velocity will not lead to modification of treatment schedule (i.e. Investigators do not have to wait for the test report to make decision regarding subsequent treatment continuation or modification) unless the symptom is deemed as clinical significant.

5.10. Appropriateness of Measurements

The measurements used in this in study are considered appropriate for the indication studied. Disease response is a common tool used in cancer trials to study the effectiveness of the study drug. Safety and tolerability of the study drug will be reported during the trial.

6. Safety and Efficacy Variables

6.1. Efficacy Measurements

Tumor response will be assessed by using computerized tomography (CT) or MRI scans according to RECIST v1.1 at baseline and at the end of Cycle 3 (at C3D21/EOT visit). For subjects who are continuing treatment beyond 3 cycles (9 weeks), tumor assessment will be performed at every three cycles until progression of disease (i.e. at or prior to Day 1 of Cycles 4, 7, 10 and so on). Any additional assessments can be arranged when clinically indicated.

Scans must include brain, chest, abdomen, and pelvis. The imaging technique used at baseline should be used throughout the study.

Subjects will be considered evaluable for tumor assessment in this study if they fulfill the criteria for evaluation according to RECIST v1.1, i.e., those subjects who undergo a baseline disease assessment within 4 weeks of treatment initiation, and who undergo at least 1 disease assessment on study (the following should be revised if revision in corresponding part in synopsis is accepted) .

- ORR is defined as the percentage of subjects who have achieved confirmed CR and PR at a particular time point after first treatment, according to RECIST v1.1.
- PFS is defined as the time from the start of treatment up to the date of first progression based on RECIST v1.1 or the date of death, whichever comes first.
- OS is defined as the as the time from the start of treatment up to the time that the subject is still alive.
- Best overall tumor response defined as an objective response or stable disease of treatment phase.

Survival data will be collected throughout the active treatment phase and during the follow-up period. Survival follow-up after subject discontinuation of treatment will be conducted every 3 weeks during the first 9 weeks, thereafter every 9 weeks until the end of the study.

6.2. Dose Limiting Toxicity (DLT)

All toxicities will be classified according to the NCI Common Terminology Criteria for AEs (CTCAE) version 4.03.

DLT will be defined as the occurrence of any of the following criteria unless there is definitive alternative evidence that administration of SCB01A did not cause the specific toxicity:

- Grade 4 neutropenia exceeding 5 days' duration
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Grade 3 or greater neutropenia with complications (e.g., fever, infection etc.)

- Grade 3 or greater thrombocytopenia with complications (e.g., bleeding)
- Grade 3 or greater non-hematological AEs including Grade 3 unmanageable nausea and vomiting that persist for 3 or more days after drug administration. Grade 3 fatigue lasting for ≤1 week is not considered as a DLT
- Grade 3 or greater prolonged QTc interval
- Grade 3 or greater neurotoxicity
- Delayed treatment exceeding 14 days duration due to drug-related toxicity.
- Not able to recover from grade 2 neurotoxicity exceeding 3 weeks

6.3. Safety Measurements

The following safety assessments will be done during the study:

- Incidence and intensity of AEs evaluated using the CTCAE version 4.03
- Incidence and intensity of clinically significant abnormal laboratory values evaluated using the CTCAE version 4.03
  - Percentage of subjects experiencing dose adjustments, including delays or omissions or discontinuation of study medication
- Physical examination findings
- Vital signs measurements
- ECG (including PR, QRS, QTc intervals) findings
- Nerve conduction velocity examination (baseline for all subjects; symptom occurring and end of the study for subjects with grade 2 or greater neurological symptom)

6.4. Pharmacokinetic Measurements

PK will only be performed on subjects enrolled in Stage I.

- PK blood samples will be taken immediately pre-infusion then at 24, 25, 26, 28 and 32 hours after start of infusion on Days 1 and 8 of Cycle 3 if dose level of Cycle 3 is 24 mg/m^2 (time window at each sample collected: ±5 min).
- Blood samples will be collected, using 10 mL sodium heparin Vacutainer® tubes. The tube will be gently inverted to ensure adequate mixing of the blood sample and anticoagulant. Samples will be placed on ice until separation and must be centrifuged within 20 minutes of collection. A precise record of blood sample collection times must be maintained on the appropriate source document.
- Plasma samples will be analyzed via a validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) method for SCB01A.

7. Adverse Events Definitions and Reporting

7.1. Adverse Events

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the medicinal product (definition per ICH E2A and E6 R1).

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology on the AE CRF page. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

For all AEs, the Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see Section on SAEs) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE.

Interventions for pre-treatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrolment are not considered AE.

7.1.1. Intensity Assessment

The severity of the AE will be graded according to the NCI Common Terminology Criteria for AEs (CTCAE) Grading Scale Version 4.03 (Publish Date: May 28, 2009, http://ctep.cancer.gov/reporting/ctc.html).

The maximum severity (intensity) of the AE will be categorized by the Investigator as follows:

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

For AEs not covered by NCI CTCAE, the severity will be characterized as "mild," "moderate," or "severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities
- Severe events interrupt the subject's usual daily activities.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates). All AEs, due to any cause that occurs during the investigation, whether or not related to the study drug, should be reported to the Safety Coordinator.

7.1.2. Causality Assessment

The investigator will assign a relationship to the study drug (i.e. causality) for all AEs that occur during the study using the definitions below:

- **Unrelated:** The AE is clearly related to other causes such as participant's clinical state, environmental factors, or other therapies administered.
- **Unlikely to be related:** The AE does not follow a reasonable temporal sequence from study drug administration; could readily have been produced by other causes such as the participant's clinical state, environmental factors, or other therapies administered; does not follow a known response pattern to the study drug.
- **Possibly related:** The AE follows a reasonable temporal sequence from study drug administration; follows a known response pattern to the study drug; could readily have been produced by other causes such as the participant's clinical state, environmental factors, or other therapies administered.
- **Probably related:** The AE follows a reasonable temporal sequence from study drug administration; follows a known response pattern to the study drug; cannot be reasonably explained by other factors such as the participant's clinical state, environmental factors, or other therapies administered; improvement upon cessation of test drug.
- **Definitely related:** The AE follows a reasonable temporal sequence from study drug administration; follows a known response pattern to the study drug; cannot be reasonably explained by other factors such as the participant's clinical state, environmental factors, or other therapies administered; improvement upon cessation of test drug or reappears upon repeat exposure (if rechallenge occurs).

7.2. Adverse Event Reporting

All AEs occurring during the study (from the time of the first study treatment until 28 days after the last dose of study treatment) observed by the Investigator or reported by the subject (whether or not attributed to study drug), will be reported on the CRF. Clinically significant AEs considered related or non-related to the IP by the Investigator or the Sponsor will be followed until resolved or considered stable by the Investigator. The following information must be provided: description; dates of onset and resolution; severity; assessment of relatedness to IP, other suspect drug, or device; and action taken. The investigator may be asked to provide follow-up information.

All AEs, serious or not, that result in the subject's permanent withdrawal of IP or from the study will be discussed between the investigator and medical monitor. The CRF for EOT/Early Withdrawal Visit should be completed including reason of withdrawal.

It will be the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from study treatment. A subject may also voluntarily withdraw from study treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo EOT assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

7.3. Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that at any dose (ICH E2A and E6 R1):

- 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 inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the sponsor's assessment. If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

All SAEs must be reported to the sponsor or sponsor designee immediately after the Investigator becomes aware of the event, along with a determination as to whether it is associated with the IP or any other study procedure.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the SAE definition.

7.4. Serious Adverse Event Reporting

All SAEs, irrespective of relationship to IP, must be reported within 24 hours of the Investigator knowledge of the event to the Sponsor or CRO. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to follow-up information on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases.

Relevant medical records should be provided to the Sponsor or CRO as soon as they become available; autopsy reports should be provided for deaths if available. Should an Investigator be made aware of an SAE occurring any time after the reporting period, it must be promptly reported.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the IP or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

7.5. Pregnancies

All initial reports of pregnancy must be reported to the Sponsor within 24 hours of the Investigator knowledge of the event using the appropriate pregnancy form.

For IP, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed (e.g., environmental exposure) to the IP, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the IP (maternal exposure) for 28 days after last dose of or exposure to IP.

- A male partner of a pregnant female has been exposed to the IP, either due to treatment or environmental exposure, within 3 months prior to the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the IP or exposure as defined above, the Investigator must submit this information on a Pregnancy form to the Sponsor (or its designated representative). In addition, the Investigator must submit information regarding environmental exposure to an IP in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Pregnancy form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see following information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all exposure during pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination (e.g., induced abortion) and then notify the Sponsor or its designated representative of the outcome as a follow-up to the initial Pregnancy form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [including that in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the neonatal death as related to exposure to IP.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8. Statistical Methods and Determination of Sample Size

8.1. Statistical and Analytical Plans

A brief description is given of the planned analysis methodology. Detailed descriptions of the statistical analysis methods and data conventions will be provided as a separate document; i.e., the Statistical Analysis Plan (SAP). The SAP may also include additional exploratory analyses not explicitly mentioned in the following sections. A detailed SAP will be finalized prior to final data base lock. Any significant changes to the analyses described in this protocol will be addressed in the SAP and the Clinical Study Report.

8.2. Determination of Sample Size

Assumption of sample size calculation:

- Study design: Simon's optimal two stage design[1]
- Type I error (one-sided): 5%
- Power: 80%
- Response probability of null hypothesis (P0): 0.05
- Response probability of SCB01A (P1): 0.20

According to these hypotheses, up to 37 subjects need to be recruited into the study (including 10 evaluable subjects in the Stage I and 19 evaluable subjects in Stage II, with the additional 8 subjects to account for replacement of subjects those who withdraw, i.e. dropout rate is 20%). At least 4 subjects are required to achieve CR or PR after treatment with SCB01A for the study to meet its primary objective. The trial will be discontinued if no objective response is observed after the Stage I tumor assessment review.

Stopping rule: The study will be stopped early for futility if less than 1/10 evaluable subjects showed ORR in Stage I; with no further investigation of the drug is less than 4/29 evaluable subjects achieve ORR by the end of Stage II.

8.3. Populations for Analysis

Subjects will be categorized into the following populations for analysis:

ITT population: The ITT population consists of all subjects enrolled in the study and received at least one study treatment.

Per-protocol (PP) population: The PP population will consist of all subjects who completed at least 3 cycles of study treatment regimen, have measurable baseline disease and at least one post-baseline RECIST assessment (PD, SD, PR or CR). Subjects with a major protocol violation, or AE, deemed by the Medical Monitor to have an impact on the study endpoints will be excluded from the PP population.

PK population: The PK population will consist of all subjects in stage I who received, at least, one dose of 24 mg/m^2 of SCB01A with sufficient post-dose bio-samples collected for PK profile characterization.

Details of any other populations for analysis will be described in the SAP.

8.4. Safety Analysis

Safety profile will be evaluated by the following endpoints.

- Incidence and intensity of AEs evaluated using the CTCAE version 4.03
- Incidence and intensity of clinically significant abnormal laboratory values evaluated using the CTCAE version 4.03
    - Percentage of subjects experiencing dose adjustments, including delays or omissions or discontinuation of study medication
- Physical examination findings
- Vital signs measurements
- ECG (including PR, QRS, QTc intervals) findings
- Nerve conduction velocity examination (baseline for all subjects; symptom occurring and end of study for subjects with grade 2 or greater neurological symptom)

All safety endpoint data will be listed and summarized for each dose and day within cycle using descriptive statistics. The change from baseline data for the safety endpoints will also be summarized using descriptive statistics.

Number and percentage of subjects experiencing at least one DLT or AE will be tabulated by dose. Further details regarding any DLTs or AEs experienced will be provided in data listings. All recorded AEs will be listed and tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) and by dose level. The incidence of Treatment Emergent AEs (TEAEs) during the study period will be tabulated by dose group, body system, and preferred term. TEAEs are those events that occur or worsen on or after first dose of IP and up to 28 days after the last dose. TEAEs are AEs with onset dates on or after the first dosing date. Those with missing onset dates will be included as treatment emergent. Number and percentage of subjects who withdrew/stopped dosing will be tabulated. Number and percentage of subjects who missed 1 or more doses (1 dose, 2 doses, etc.) in any cycle will be tabulated by cycle.

Serious AEs, Grade 3 and above AEs, AEs related to study treatment, and AEs causing discontinuation will be tabulated. AEs for individual subjects will be listed, along with information regarding onset, duration, severity, and relationship to study treatment.

Vital signs, physical examination, ECG, and clinical laboratory test results will be listed and summarized by dose group, cycle and day within cycle as applicable and may be presented graphically. Any significant or outside normal range limits value for vital signs, physical examination, ECG, or clinical laboratory results will be listed.

8.5. Efficacy Analysis

The primary efficacy analysis will be performed to assess the Objective Response Rate (ORR) and secondary efficacy analysis will be performed to assess the PFS, overall survival rate and the best overall tumor response.

Inferential analysis results will be expressed as point estimates and their 95% CIs. Analyses will be carried out using SAS® Software, version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

All time-to-event endpoints, including OS and PFS, will be reported in days (median with 95% CI and range) and calculated using Kaplan-Meier methods. Subjects who have not progressed or who have not died at the time of the analysis will be censored at the last assessment date.

The study will be stopped early for futility if less than 1/10 showed ORR in Stage I; with no further investigation of the drug is less than 4/29 achieve ORR by the end of Stage II.

8.6. PK Analysis

The blood samples will be assayed for SCB01A and PK parameters (maximum plasma concentration [C_{max}], clearance [CL], volume of distribution [Vd], half-life [$t_{1/2}$], elimination constant [K_{el}], mean residence time [MRT] and time to maximum concentration [T_{max}]) will be determined and presented graphically and descriptively (as appropriate).

8.7. Interim Analysis

An interim statistical analysis will be performed following the completion of stage I. The study will be stopped early for futility if less than 1/10 showed ORR in Stage I; with no further investigation of the drug is less than 4/29 achieve ORR by the end of Stage II.

9. Study Management

9.1. Regulatory Guidelines

The study will be performed in accordance with US Investigational New Drug (IND) regulations (21 Code of Federal Regulations [CFR] 56) or local national laws (as applicable), the guidelines of ICH, and the guidelines of the declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and amended by subsequent assemblies (see Section 11.2 [Appendix 2]).

9.2. Ethics

9.2.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Before implementing this study, the protocol, the proposed informed consent forms (ICFs) and other information for the subjects, must be reviewed by a properly constituted committee(s) responsible for approving clinical studies. The IRB/IEC written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title, date and version number), and of the ICF (date, version).

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor and the IRB/IEC.

9.2.2. Ethical Conduct of the Study

The study will be conducted in accordance with the approved study protocol and SOPs of the Sponsor or CRO that meet the guidelines provided by the ICH E6 for GCP in clinical studies.

9.3. Subject Information and Consent

The investigator must fully inform the subject of all pertinent aspects of the trial including the written information approved by the IRB/IEC.

Prior to the start of screening, the written ICF must be signed and personally dated by the subject and by the investigator who conducted the informed consent discussion. One copy of the written information and signed consent form must be given to each subject and one copy must be retained in the investigator's study records.

9.4. Confidentiality and Disclosure

Data on subjects collected on CRFs during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial subjects. All parties involved in

the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a subject participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

All information provided to the investigator by the Sponsor, or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than the Sponsor, or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

9.5. Indemnification

The sponsor's indemnification of the investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as required under local regulations.

9.6. Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

9.7. Study Documentation

By signing a copy of Form FDA 1572 or other country-specific regulatory forms, the Principal Investigator acknowledges that he/she has received a copy of the Investigator's Brochure (IB) on the IP and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572 and other country-specific forms. No changes in this protocol can be made without the Sponsor's written approval.

The Investigator will supply the Sponsor with the following documents:

- Original, signed Form FDA 1572 and other country-specific forms
- Curricula vitae for all Investigators listed on Form FDA 1572 and other forms
- Copy of Principal Investigator's medical licensure/medical registration number
- Signed protocol signature page
- List of IRB/IEC members and their occupations/affiliations or multiple assurance number
- Letter indicating IRB/IEC approval to conduct the protocol
- Copy of IRB/IEC-approved ICF

The Sponsor will supply the Investigator with the following documents:

- Clinical study protocol
- IB
- Sample ICF
- CRFs/instruction manual
- Laboratory certification records and reference ranges, if applicable
- Insurance certificate

9.8. Data Handling and Record Retention

9.8.1. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

9.8.2. Recording and Collection of Data

All source documents and CRFs will be completed as soon as possible after the subject's visit. Corrections to data on the source will be documented. The investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

9.8.3. Clinical Data Management

The sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the sponsor's or CRO's SOPs for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH GCP, and local regulations where applicable) and the sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

9.8.4. Archiving

The investigator must make original study data (paper or electronic) accessible to the study monitor, other authorized sponsor representatives, and regulatory agency inspectors (e.g., US FDA) upon request. A file for each subject must be maintained that includes the signed ICF and copies of all source documentation related to that subject. The investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

Subject identity information recorded will be maintained for at least 15 years on the subject confidentiality log or longer if required by local regulations.

Investigators must maintain all study documentation for at least 2 years following the approval of the drug, or until 2 years after the investigational drug program is

discontinued, or longer if required by local regulations. Study documentation includes all essential documents as defined in ICH E6 Guidelines for GCP. The sponsor or designee will notify the investigator when any records may be discarded, but investigators must comply with local regulations.

9.9. Monitoring

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the period of the study. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the CRFs.

The investigator will make available source documents, medical records, and source data necessary to complete CRFs to the monitor. In addition, the investigator will work closely with the monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

9.10. Protocol Amendments, other Changes in Study Conduct

9.10.1. Protocol Amendments

Any changes to the study protocol will be addressed in a Protocol Amendment which will receive IEC approval before implementation thereof.

9.10.2. Other Changes in Study Conduct

Any other changes to the study conduct or statistical analyses will be described in the clinical study report.

9.11. Quality Control and Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

Audits may be conducted at the discretion of the sponsor as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, SOPs, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. If such an audit occurs, the investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

9.12. Publication Policy

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study will be published in a relevant peer- reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor. No publications will be allowed without the agreement of the Sponsor.

10. References

[1] Simon R, 1989. Optimal Two-Stage Designs for Phase II Clinical Trials. Controlled Clinical Trials. 10: 1-10.

[2] Cooney, MM., Heeckeren, W., Shyam, B., et al. Drug Insight: Vascular disrupting agents and angiogenesis-novel approaches for drug delivery. *Nat Rev Clin Oncology.* 2006; 3: 682-692.

[3] Tozer, GM., Kanthou, C., & Baguley, BC. Disrupting tumor blood vessels. *Nat Rev Cancer.* 2005; 5(6): 423-435.

[4] Mosteller RD. "Simplified calculation of body-surface area". *N Engl J Med* 1987; 317:1098. PMID 3657876.

[5] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*1982;5:649-655

11. Appendices

11.1. Appendix 1 – Reference List of Known Inhibitors of CYP1A2 and CYP2D6 Inhibitors

1A2	2D6
Strong fluvoxamine ciprofloxacin **Weak** cimetidine **Others** amiodarone efavirenz fluoroquinolones fluvoxamine furafylline1 interferon methoxsalen mibefradil ticlopidine	**Strong** bupropion cinacalcet fluoxetine paroxetine quinidine **Moderate** duloxetine sertraline terbinafine **Weak** amiodarone cimetidine **Others** celecoxib chlorpheniramine chlorpromazine citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine haloperidol histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine ranitidine reduced-haloperidol ritonavir ticlopidine tripelennamine

A **Strong** inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
A **Moderate** inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
A **Weak** inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

URL: http://medicine.iupui.edu/clinpharm/ddis/main-table/

11.2. Appendix 2 – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION (WMA) DECLARATION OF HELSINKI

Ethical Principles for Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they

have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific

principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.