SynCoreBio

Protocol Number: SCB01A-21

# An Open-Label, Phase II Study to Evaluate SCB01A in Patients with Recurrent or Metastatic Squamous Cell Head and Neck Cancer who have Received Platinum-Based Treatment

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| Author(s): | SynCore Biotechnology Co., Ltd. |
| Investigational Product: | SCB01A |
| Development Phase: | Phase II |
| Version/Date: | Version 3.0 /25 Jul 2016 |

SynCore Biotechnology Co., Ltd.
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Taiwan, R.O.C.

## INVESTIGATOR SIGNATURE PAGE

## STUDY ACKNOWLEDGEMENT

**An Open-Label, Phase II Study to Evaluate SCB01A in Patients with Recurrent or Metastatic Squamous Cell Head and Neck Cancer who have Received Platinum-Based Treatment**

**SCB01A**

# Amendment 3

**25 Jul 2016**

## 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.

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| Investigator Name (Printed) | Institution |
| Signature | Date |

**Please retain the original for your study files.**

# Signature Page for Sponsor

**Protocol Number:** SCB01A-21

**Protocol Title:** An Open-Label, Phase II Study to Evaluate SCB01A in Patients with Recurrent or Metastatic Squamous Cell Head and Neck Cancer who have Received Platinum-Based Treatment

**SynCoreBio Approval(s):**

Muh-Hwan Su
General Manager
SynCore Biotechnology Co., Ltd.

| Signature | Date |
|---|---|

Hui-Hung Wang
Head of Project management
SynCore Biotechnology Co., Ltd.

| Signature | Date |
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Chien-Chang Su
Project Manager
SynCore Biotechnology Co., Ltd.

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Shoung-Hui Tsai
Quality Assurance
SynCore Biotechnology Co., Ltd.

| Signature | Date |
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Ronelle Heath
Biostatistician, Data Management
Novotech Australia PTY LTD

| Signature | Date |
|---|---|

SUMMARY OF MAJOR PROTOCOL AMENDMENT CHANGES

**Amendment 3**

In addition to the major changes listed below, minor editorial changes were made throughout the document to correct typographical errors, and to improve consistency and clarity.

| Page | Version: 2.0 (Date: Apr-8-2015) | Version: 3.0 (Date: 25-Jul-2016) | Reason/Rationale for the change |
|---|---|---|---|
| 1 | Version/Date: Version 2.0/ 08-Apr-2015 | Version/Date: Version 3.0/ 2-Mar-2016 | Version change |
| 2 | **Signature Page for Sponsor:**<br>Chien-Chih Ou<br>Head of Project Management<br>SynCore Biotechnology Co., Ltd.<br><br>Chi-Ling Liu<br>Project Manager<br>SynCore Biotechnology Co., Ltd.<br><br>Ya-Tang Liao<br>Quality Assurance<br>SynCore Biotechnology Co., Ltd. | **Signature Page for Sponsor:**<br>**Hui-Hung Wang**<br>Head of Project Management<br>SynCore Biotechnology Co., Ltd.<br><br>**Chien-Chang Su**<br>Project Manager<br>SynCore Biotechnology Co., Ltd.<br><br>**Shoung-Hui Tsai**<br>Quality Assurance<br>SynCore Biotechnology Co., Ltd. | Personnel change |
| 3 | **Study Rationale:**<br>The research data available to date indicate that SCB01A is a promising anticancer agent with a vascular disrupting activity that has the potential for treatment of various malignancies, particularly for patients with drug resistance to existing therapies. The drug has been trialed in human patients in an ongoing dose-escalation phase I study and shown to be safe for up to 2 cycles of 16 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 patient with right buccal squamous cell carcinoma and 15/23 (65%) patients had stable disease (SD) for more than 2 cycles. A pre-clinical study of SCB01A showed that the concentration at which tubulin inhibition occurred was 200 nM. Pharmacokinetic (PK) results demonstrated that average serum concentration of | **Study Rationale:**<br>The research data available to date indicate that SCB01A is a promising anticancer agent with a vascular disrupting activity that has the potential for treatment of various malignancies, particularly for patients with drug resistance to existing therapies. The drug has been trailed in human patients in a dose-escalation phase I study and shown to be safe for up to 2 cycles of 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 patient with right buccal squamous cell carcinoma and 19/33 (58%) patients had stable disease (SD) for more than 2 cycles. A pre-clinical study of SCB01A showed that the concentration at which tubulin inhibition occurred was 200 nM. Pharmacokinetic (PK) results demonstrated that average serum concentration of SCB01A reached | To update the maximum tolerance dose and study information from finished phase I study |

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| | SCB01A reached 600 nM at 16 mg/m$^2$ suggesting that the current dose is safe and close to its probable efficacious concentration. The aim of this Phase II study with SCB01A is to determine the effect of SCB01A in patients with squamous cell carcinoma of head and neck who have failed previous platinum based therapies. | 1000 nM at 24 mg/m$^2$ suggesting that the current dose is safe and beyond its probable efficacious concentration. Based on both observed PK profile in Phase I study and also simulation data, the administration of SCB01A at 18 and 24 mg/m2 in D1 and D8 of a 21-days cycle will extend the duration of effective concentration in blood. One subject in the 24 mg/m$^2$ cohort revealed that a higher blood concentration of SCB01A was not linked to the elevated incidence of adverse events. Besides, the severe peripheral neuropathy of one subject was clinically judged as probably related to SCB01A but also may be involved in other causes including underlying diabetic mellitus and previous cytotoxic medication. Another subject in the 32 mg/m$^2$ cohort demonstrated that resolution of lower limb weakness after one week indicating the reversal of adverse events.<br>The aim of this Phase II study with SCB01A is to determine the effect of SCB01A in patients with squamous cell carcinoma of head and neck who have failed previous platinum based therapies. | |
| **4** | **Study Design**<br><u>Run-in Phase</u><br>During the run-in phase, three patients will be enrolled and will receive 3 cycles of i.v. administration of SCB01A at a dose of 3.25 mg/m$^2$ on Days 1 and 8 of each cycle in a 3-week cycle (Dose 1). If one of the three patients experiences a dose limiting toxicity (DLT) during the first 3 cycles, an additional three patients will be enrolled at the same dose level (Dose 1).<br><br>Patients enrolled in the run-in phase must either complete 3 | **Study Design**<br><u>Run-in Phase</u><br>During the run-in phase, three patients will be enrolled to receive 3 cycles of i.v. SCB01A at a dose of 3.25 mg/m$^2$ (Dose 1) on Days 1 and 8 of each cycle in a 3-week cycle (Dose 1). If 1 or more of the three patients experiences a dose limiting toxicity (DLT) during the first 3 cycles, an additional three patients will be enrolled at the same dose level. If 0/3 or 1/6 i.e $\leq$1 of subjects experience DLT at the given dose level, subject can be enrolled in the next higher dose cohort, and this process will | To update the study procedures:<br>a. Add 3 more dose levels in run-in phase;<br>b. Clarify the dose escalation and de-escalation procedures in run-in phase; |

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| | cycles of study treatment or experience a DLT to be included in the Full Analysis Set (FAS) for the statistical analyses. During the run-in phase, patients who do not complete the 3 cycles of study treatment, and who do not experience a DLT, will be replaced. | continue until >1/6 of subjects experience DLT at certain dose level or the maximum dose in this protocol, 24 mg/ $m^2$ (Dose 4) is reached.<br><br>Patients enrolled in the run-in phase must either complete 3 cycles of study treatment or experience a DLT to be included in the Full Analysis Set (FAS) for the statistical analyses. During the run-in phase, patients who do not complete the 3 cycles of study treatment, and who do not experience a DLT, will be replaced.<br><br>Rules for dose escalation for the run-in phase of the study are listed as following:<br>1. Dosing will start at 3.25 mg/$m^2$ (Dose 1) in the 1st Cohort and can be escalated to 12 mg/$m^2$ (Dose 2), 18 mg/$m^2$ (Dose 3) and 24 mg/$m^2$ (Dose 4). If ≤1 subjects have DLT in a cohort of 24 mg/$m^2$ (Dose 4), the 24 mg/$m^2$ (Dose 4) will be determined as the Optimal Dose.<br>2. If =1/3 subjects in a cohort have DLT(s), three more subjects to be enrolled at the same dose level or if ≤1 subjects (i.e 0/3 or 1/6) experience DLT then subjects can be enrolled into the next higher dose level as per below:<br>Dose Level 3.25 mg/$m^2$ (Dose 1): *Note: Dose 1 cohort has been completed and no DLT seen, thus enrolment to start at Dose level 2 under current Protocol Amendement 3.*<br>a) Dose Level 12 mg/$m^2$ (Dose 2): If 1 patient experiences DLT then 3 | |

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| | | additional patients to be enrolled in the same dose level. If the total DLT from 6 patients in the same dose level is ≤1 then move to the next higher dose level. If >1 patients have DLT then 3 patients to be enrolled at reduced dose of 10mg/ $m^2$ (Dose 1a). If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If ≤1 patient has DLT then dose level 10mg/ $m^2$ (Dose 1a) will be considered Optimal Dose. If >1 patients have DLT then dose will be further reduced to 5 mg/$m^2$ (Dose 0a) for the next 3 patients enrolled in the study. If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If ≤1 has patient DLT then dose level 5 mg/$m^2$ (Dose 0a) will be considered Optimal Dose. If >1 patients have DLT then 3.5 mg/$m^2$ (Dose 1) will be considered MTD.<br>b) Dose Level 18 mg/$m^2$ (Dose 3): If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If the total DLT from 6 patients in the same dose level is ≤1 then move to the next higher dose level. If >1 patient has DLT then 3 patients to be enrolled at reduced dose of 15mg/ $m^2$ (Dose | |

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| | | 2a). If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If ≤1 patient has DLT then dose level 15mg/ $m^2$ (Dose 2a) will be considered Optimal Dose. If >1 patient have DLT then 12 mg/$m^2$ (Dose 2) will be considered MTD.<br>c) Dose Level 24 mg/$m^2$ (Dose 4): If 1 patient experiences DLT then enrol 3 additional patients in the same dose level. If the total DLT from 6 patients at the same dose level is ≤1 then Dose Level 24 mg/$m^2$ (Dose 4) will be the Optimal Dose. If >1 patient have DLT then 3 patients to be enrolled at the reduced dose of 21mg/ $m^2$ (Dose 3a). If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If ≤1 patient has DLT then dose level 21mg/ $m^2$ (Dose 3a) will be considered Optimal Dose. If >1 patients have DLT then 18 mg/$m^2$ (Dose 3) will be considered MTD.<br><br><u>Phase II</u><br>In the phase II of the study additional patients will be enrolled to evaluate the Optimal Dose as established by review of the safety committee.<br>a) Stage 1: In stage 1 of phase II, 7 subjects to be | |

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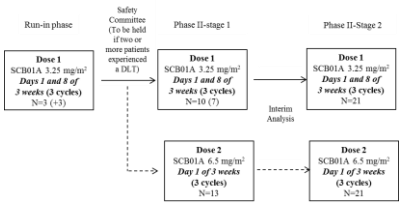
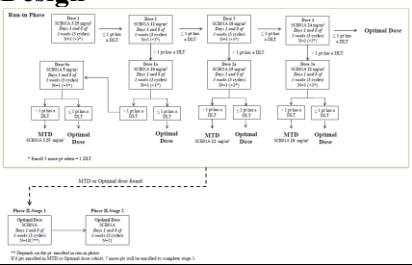
| | | enrolled and dosed at the optimal dose level as established by the safety review committee. *Note:* In case only 3 patients were enrolled in the optimal dose cohort of the run-in phase then 10 patients to be enrolled in stage 1 thus enrolling total 13 subjects in the optimal dose level.<br>b) Stage 2: Once all subjects have completed their treatment cycle in stage 1 then a review by safety committee will be conducted to confirm if stage 2 can be initiated. If confirmed then stage 2 of the study will enrol additional 21 subjects who will be dosed at the same Optimal Dose level identified for stage 1. | |
| **5** | **Figure 1 Schematic Study Design**<br>  | **Figure 1 Schematic Study Design**<br>  | To update the schematic study design |
| **6** | A safety committee will be established to:<br>1. Evaluate all AEs, and laboratory safety data for the run-in phase;<br>2. Decide on the recommended dose regimen of SCB01A for Phase II (Dose 1 or Dose 2). | A safety committee will be established to:<br>1. Evaluate all AEs, and laboratory safety data for the run-in phase;<br>2. Decide on the recommended dose regimen of SCB01A for Phase II (Optimal Dose). | To revise the of function of safety committee in defining Optimal Dose |
| **7** | **Number of Planned Patients:**<br>Up to 40 patients will be enrolled, consisting of 3 to 6 patients in the run-in phase; 7 to 10 patients at Dose 1 or 13 patients at Dose 2 in stage 1 of Phase II and 21 patients | **Number of Planned Patients:**<br>Up to 64 patients will be enrolled, consisting up to 30 patients in the run-in phase; 7 to 10 patients at Stage 1 of Phase II at the 'Optimal Dose' and 21 patients in Stage 2 | To update the definition of optimal dose |

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| | in Stage 2 of Phase II. During the run-in phase, any patients who do not complete the 3 cycles of study treatment, and do not experience a DLT, will be replaced, while no patients will be replaced during Phase II. | of Phase II assuming replacement of 20% of patients in the run-in Phase. During the run-in phase, any patients who do not complete the 3 cycles of study treatment, and do not experience a DLT, will be replaced, while no patients will be replaced during Phase II. | |
| **8** | **Investigational Product:**<br>Name: SCB01A<br>Dose and Route of Administration<br>• Dose 1: one i.v. administration of 3.25 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 2: one i.v. administration of 6.5 mg/m$^2$ SCB01A on Day 1 of a 3-week cycle. | **Investigational Product:**<br>Name: SCB01A<br>Dose and Route of Administration will be one of the following:<br>• Dose 1: one i.v. administration of 3.25 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 0a : one i.v. administration of 5 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 1a : one i.v. administration of 10 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 2: one i.v. administration of 12 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle<br>• Dose 2a : one i.v. administration of 15 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 3: one i.v. administration of 18 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 3a : one i.v. administration of 21 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or<br>• Dose 4: one i.v. administration of 24 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle or | To revise the proposed study dose |
| **9** | According to a PP approach, all enrolled patients who meet the eligibility criteria and do not present major deviations during the study will be included in the analyses. Inferential analysis results will be expressed as point estimates and their 95% | Both according to FAS and PP approaches (all enrolled patients who meet the eligibility criteria and do not present major deviations during the study) will be included in the analyses. The conclusion will be summarized according to analyses of PP | To revise the proposed statistical methods |

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| | confidence intervals (CIs). To be consistent with the sample size calculation, the 90% CI will also be presented. Analyses will be carried out using SAS® Software, version 9.3 or higher (SAS Institute, Cary, North Carolina, USA). | population. Inferential analysis results will be expressed as point estimates and their 95% confidence intervals (CIs). To be consistent with the sample size calculation, the 90% CI will also be presented. Analyses will be carried out using SAS® Software, version 9.3 or higher (SAS Institute, Cary, North Carolina, USA). | |
| **10** | **Duration of the Study:**<br>The planned duration of the entire study is approximately 24 months with an enrolment period of 6 months. | **Duration of the Study:**<br>The planned duration of the entire study is approximately 30 months with an enrolment period of 12 months. | To update the duration of the study |

# Table of Contents

## Tables

## Figures

# LIST OF ABBREVIATIONS:

| Abbreviation | Definition |
|---|---|
| AE(s) | Adverse Event(s) |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Aminotransferase |
| $AUC_{0-inf}$ | Area Under the Plasma Concentration-time Curve from Time Zero to Infinite Time |
| $AUC_{0-t}$ | Area Under the Plasma Concentration-time Curve from Time Zero to Time t |
| BSA | Body Surface Area |
| CEC | Circulating Endothelial Cells |
| CEP | Circulating Endothelial Progenitor |
| Ck | Creatine Kinase |
| CL | Clearance |
| $C_{max}$ | Maximum Plasma Concentration |
| CR | Complete Response |
| CRO | Clinical Research Organization |
| CT | Computerized Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCE-MRI | Dynamic Contrast-Enhanced MRI |
| DLT | Dose Limiting Toxicity |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EORTC QLQ | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire |
| EOT | End of Treatment |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GGT | Gammy Glutamyltransferase |
| Hb | Hemoglobin |
| HDL | High-density Lipoprotein |
| HPLC/MS-MS | High-Performance Liquid Chromatography/Tandem Mass Spectrometry |
| HPV | Human Papillomavirus |

| Abbreviation | Definition |
|---|---|
| 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 |
| 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 |
| NCV | Nerve Conduction Velocity |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| PR | Partial Response |
| PT | Prothrombin |
| RBC | Red Blood Cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| 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 |
| VEGF | Vascular Endothelial Growth Factor |

| Abbreviation | Definition |
|---|---|
| WBC | White Blood Cell |

## SYNOPSIS

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|---|---|
| **Title of Study:** | An Open-Label, Phase II Study to Evaluate SCB01A in Patients with Recurrent or Metastatic Squamous Cell Head and Neck Cancer who have Received Platinum-Based Treatment |
| **Sponsor:** | SynCore Biotechnology Co., Ltd. No. 84 Chung-Shan Rd., Chung-Shan Village, Tung-Shan Shine, ILan, Taiwan, R.O.C. |
| **Principal/ Coordinating Investigator:** | Dr. Cheng-Hsu Wang, Director, Keelung Chang Gung Cancer Center, Keelung Chang Gung Memorial Hospital, Keelung, Taiwan |
| **Investigational Product (IP):** | SCB01A |
| **Protocol Number:** | SCB01A-21 |
| **Indication:** | Recurrent or metastatic squamous cell carcinoma of head and neck |
| **Phase of Development:** | Phase II |
| **Study Centers:** | 4–8 sites in Taiwan |
| **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 patients 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 patient with right buccal squamous cell carcinoma and 19/33 (58%) patients had stable disease (SD) for more than 2 cycles.<br><br>Pre-clinical study of SCB01A showed that the concentration at which tubulin inhibition occurred was 200 nM. Pharmacokinetic (PK) results demonstrated that average serum concentration of SCB01A reached 1000 nM at 24 mg/m$^2$ suggesting that the current dose is safe and beyond its probable efficacious concentration. Based on both observed PK profile in Phase I study and also simulation data, the administration of SCB01A at 18 and 24 mg/m2 in D1 and D8 of a 21-days cycle will extend the duration of effective concentration in blood. One subject in the 24 mg/m$^2$ cohort revealed that a higher blood concentration of SCB01A was not linked to the elevated incidence of adverse events. Besides, the severe peripheral neuropathy of one subject was clinically judged as probably related to SCB01A but also may be involved in other causes including underlying diabetic mellitus and previous cytotoxic medication. Another subject in the 32 mg/m2 cohort demonstrated that resolution of lower limb weakness after one week indicating the reversal of adverse events.<br><br>The aim of this study is to determine the effect of SCB01A in patients |

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| | with squamous cell carcinoma of head and neck who have failed previous platinum based therapies. |
| **Study Objectives:** | **Objective:**<br><br>The study is designed with a run-in phase and the continuation phase (Phase II) is to evaluate the safety and efficacy of SCB01A in patients with recurrent or metastatic squamous cell carcinoma of head and neck.<br><br>**Run-in phase**<br><br>***Primary Objective:***<br><br>To determine the optimal dose for 3 cycles of i.v. administration of SCB01A on Days 1 and 8 of each cycle in a 3-week cycle<br><br>***Secondary Objective:***<br><br>To evaluate the safety and toxicity for 3 cycles of i.v. administration of SCB01A on Days 1 and 8 of each cycle in a 3-week cycle<br><br>**Phase II**<br><br>***Primary Objective:***<br><br>To assess the disease control rate (DCR) at the end of the 9$^{th}$ week (3 cycles, each cycle consists of 21 days) after treatment with SCB01A, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.<br><br>***Secondary Objectives:***<br><br>• To assess the overall survival (OS) rate at 36 weeks after first treatment with SCB01A in patients with recurrent or metastatic squamous cell head and neck cancer who have previously been treated with platinum therapy.<br>• To assess the progression-free survival (PFS)<br>• To assess the PK profile of SCB01A of patients in the run-in phase.<br>• To assess health outcomes using patient-reported European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and EORTC QLQ H&N35 questionnaires.<br>• To assess biomarkers relevant to the efficacy and mechanism of action of SCB01A.<br>• To explore the possible association between biomarkers and clinical outcomes |
| **Study Design:** | Multicenter, open-label, phase II study of SCB01A administered to patients with recurrent or metastatic squamous cell carcinoma of head and neck. The study will be conducted in two parts.<br><br>**Run-in Phase I (Dose Escalation Phase):** |

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| | The first part of the study involves dose-escalation, in which successive cohorts of three patients (expanded to six patients in the event of a dose-limiting toxicity) will receive escalating doses of SCB01A until 24 $mg/m^2$. Dose escalation assessment will be based on tolerability observed during 3 cycles of treatment. An Optimal Dose will be agreed upon.<br><br>During the run-in phase, three patients will be enrolled and will receive 3 cycles of i.v. administration of SCB01A at a dose of 3.25 $mg/m^2$ (Dose 1) on Days 1 and 8 of each cycle in a 3-week cycle (Dose 1). If 1 of the three patients experiences a dose limiting toxicity (DLT) during the first 3 cycles, an additional three patients will be enrolled at the same dose level. If 0/6 or 1/6 i.e ≤1 of subjects experienced DLT at the given dose level, the dose of the subsequent cohort will be increased to the next level, then this process will continue until >1/6 of subjects experience DLT at certain dose level or the maximum dose in this protocol, 24 $mg/m^2$ (Dose 4) is reached.<br><br>Patients enrolled in the run-in phase must either complete 3 cycles of study treatment or experience a DLT to be included in the Full Analysis Set (FAS) for the statistical analyses. During the run-in phase, patients who do not complete the 3 cycles of study treatment, and who do not experience a DLT, will be replaced.<br><br>Rules for dose escalation for the run-in phase of the study are listed as following:<br>1. Dose level will start at 3.25 $mg/m^2$ (Dose 1) in the 1st Cohort and can be escalated to 12 $mg/m^2$ (Dose 2), 18 $mg/m^2$ (Dose 3) and 24 $mg/m^2$ (Dose 4). If ≤1 subjects have DLT in a cohort of 24 $mg/m^2$ (Dose 4), the 24 $mg/m^2$ (Dose 4) will be determined as the Optimal Dose.<br>2. If =1/3 subjects in a cohort have DLT(s), enrol three more subjects at the same dose level or if ≤1 subjects (i.e., 0/3 or 1/6) experience DLT then subjects can be enrolled into the next higher dose level as per below:<br>a) **Dose Level 3.25 $mg/m^2$ (Dose 1):** This dose level has been completed as part of protocol amendment #2 and ≤1 patient experienced DLT. Patients will be enrolled in the next dose level based on results from 3.25 $mg/m^2$ (Dose 1) Cohort.<br>b) **Dose Level 12 $mg/m^2$ (Dose 2):** If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If the total DLT from 6 patients at the same dose level is ≤1, then the study to move to the next higher dose level. If >1 patients have DLT, then 3 patients to be enrolled at the reduced dose of 10 $mg/m^2$ (Dose 1a).<br>c) **Dose level 10 $mg/m^2$ (Dose 1a):** If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If ≤1 patient has DLT then dose level 10$mg/m^2$ (Dose 1a) will be considered Optimal Dose. If >1 patients have DLT then dose will be further reduced to 5 $mg/m^2$ (Dose 0a) for the next 3 patients enrolled in the study. |

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| | d) **Dose level 5 mg/m$^2$ (Dose 0a):** If 1 patient experiences DLT then we enrol 3 additional patient in the same dose level. If ≤1 has patient DLT then dose level 5 mg/m$^2$ (Dose 0a) will be considered Optimal Dose. If >1 patients have DLT then 3.5 mg/m$^2$ (Dose 1) will be considered MTD.<br>e) **Dose Level 18 mg/m$^2$ (Dose 3):** If 1 patient experiences DLT then we enrol 3 additional patient in the same dose level. If the total DLT from 6 patients in the same dose level is ≤1 then we move to the next higher dose level.<br>f) **Dose Level 15 mg/m$^2$ (Dose 2a):** If >1 patient have DLT in Dose 3, then 3 patients to be enrolled at a reduced dose of 15mg/ m$^2$ (Dose 2a). If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If ≤1 patient has DLT then dose level 15mg/ m$^2$ (Dose 2a) will be considered Optimal Dose. If >1 patients have DLT then 12 mg/m$^2$ (Dose 2) will be considered MTD.<br>g) **Dose Level 24 mg/m$^2$ (Dose 4):** If 1 patient experiences DLT then 3 additional patients to be enrolled in the same dose level. If the total DLT from 6 patients at the same dose level is ≤1 then Dose Level 24 mg/m$^2$ (Dose 4) will be the Optimal Dose.<br>h) **Dose Level 21mg/m$^2$ (Dose 3a):** If >1 patient has DLT in Dose 4, then 3 patients to be enrolled at reduced dose of 21mg/ m$^2$ (Dose 3a). If 1 patient experiences DLT then 3 additional patient to be enrolled in the same dose level. If ≤1 patient has DLT then dose level 21mg/ m$^2$ (Dose 3a) will be considered Optimal Dose. If >1 patients have DLT then 18 mg/m$^2$ (Dose 3) will be considered MTD.<br><br><u>Phase II :</u><br>In the phase II of the study additional patients will be enrolled to evaluate the Optimal Dose as established by review of the safety committee.<br><br>Stage 1: In stage 1 of phase II, 7 subjects will be enrolled and dosed at the optimal dose level as established by the safety review committee.<br>*Note:* In case only 3 patients were enrolled in the optimal dose cohort of the run-in phase then 10 patients will be enrolled in stage 1 thus enrolling total 13 subjects in the optimal dose level.<br><br>Stage 2: Once all subjects have completed their treatment cycle in stage 1 then a review by safety committee will be conducted to confirm if stage 2 can be initiated. If confirmed then stage 2 of the study will enrol additional 21 subjects who will be dosed at the same Optimal Dose level identified for stage 1<br><br>No patients will be replaced in the continuation phase (Phase II). |

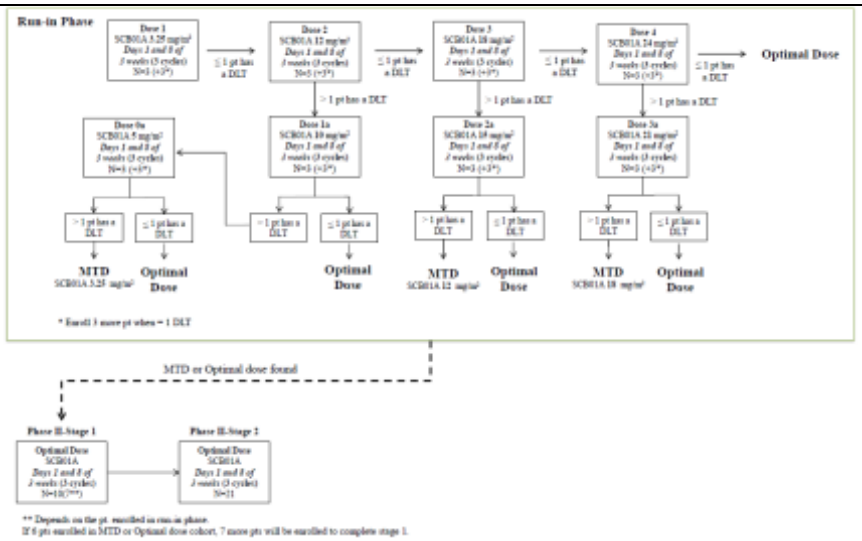


**Figure 1: Schematic Study Design**

All patients will be treated until the occurrence of progressive disease, intolerable adverse events (AEs)/toxicity, consent withdrawal or death. After discontinuation of study treatment, all patients 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, thereafter every 9 weeks until the end of the study.

The study will be completed 36 weeks after the last patient has received their 1st treatment with SCB01A.

<u>Dose Limiting Toxicity (DLT) definition (in run-in phase)</u>

- 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:
  1. Grade 4 neutropenia exceeding 5 days duration;
  2. Grade 4 thrombocytopenia;
  3. Grade 4 anemia;
  4. Grade 3 or greater neutropenia with complications (e.g., fever, infection, etc.);
  5. Grade 3 or greater thrombocytopenia with complications (e.g., bleeding);
  6. 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;
  7. Grade 3 or greater prolonged QTc interval;
  8. Grade 3 or greater neurotoxicity;
  9. Delayed treatment is exceeding 14 days duration due to drug-

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| | related toxicity.<br><br>Safety Monitoring Committee (SRC)<br><br>The SRC, composed of the principle investigators at each participating site, an independent medical monitor (physician experienced in oncology studies), and medical and safety representatives of the Sponsor, will be responsible for making decisions regarding dose escalation, determining the recommended dose, and starting enrollment of cohort expansions. Serial assessments of PK results also may be taken into account for the determination of the MTD and Optimal Dose.<br>Safety Monitoring Committee will meet after completion of Each Cohort in the Run-in Phase and after the completion of Phase II stage 1.<br><br>**MTD Definition**<br>The MTD is defined as the dose immediately preceding the dose level at which DLTs are observed in 2 or more patients. |
| **Number of Planned Patients:** | Up to 64 patients will be enrolled, consisting up to 30 patients in the run-in phase; 7 to 10 patients at Stage 1 of Phase II at the 'Optimal Dose' and 21 patients in Stage 2 of Phase II. During the run-in phase, any patients who do not complete the 3 cycles of study treatment, and do not experience a DLT, will be replaced, while no patients will be replaced during Phase II. |
| **Diagnosis and main criteria for enrolment:** | **Inclusion Criteria**:<br>1. Aged ≥20 years;<br>2. Signed informed consent obtained prior to initiation of any study-specific procedures and treatment;<br>3. Histological or cytological confirmed squamous cell carcinoma of head and neck;<br>4. Patients with non-resectable, unfeasible radiotherapy, recurrent or metastatic head and neck squamous cell carcinoma, after previous treatment with a platinum agent;<br>5. At least one measurable tumor lesion toas defined by RECIST version 1.1 as assessed by the investigator (local radiological image assessment);<br>6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-2;<br>7. Life expectancy of 12 weeks or longer;<br>8. Patients must have radiological measurable or clinically evaluable disease. Physical examination and radiographic studies have to be performed within 28 days of enrolment;<br>9. Concurrent local therapy is not allowed, but concurrent palliative radiation therapy to non-measurable sites of disease such as painful bone metastasis is permitted;<br>10. All eligible patients of childbearing potential have to use |

effective contraception; that is, double barrier contraceptive methods;

11. Documented progressive disease within past 6 months;
12. 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.
    h. Serum albumin ≥ 3 g/dL;
    i. INR ≤ 1.5 x ULN
    j. Total Bilirubin ≤ 1.5 x ULN

**Exclusion Criteria:**

1. Known primary CNS malignancy or CNS involvement (except for brain metastases that have been treated and are stable and patient is off steroids);
2. Systemic cancer therapy, Chemotherapy, radiation therapy, major surgery or investigational agents less than 4 weeks prior to study drug treatment;
3. History of malignancy other than head and neck cancer. Second primary head and neck tumors are excluded with the exception of early stage non-melanoma skin cancer or carcinoma *in situ* of cervix;
4. Ultrasound or radiological evidence of liver cirrhosis;
5. Severe pulmonary obstructive or restrictive disease;
6. Uncontrolled inflammatory disease (autoimmune or infectious);
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. Participation in another clinical trial or treatment with any investigational drug within 30 days prior to study entry;
11. QTc > 450 msec;
12. Pregnant or breast-feeding patients, and men and women of child-bearing potential not using effective contraception while on study treatment;Known hypersensitivity to any component of SCB01A;

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| | 13. History of exposure to SCB01A or its analogues;<br>14. 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;<br>15. Any other reason the investigator deems the patient to be unsuitable for the study |
| **Duration of Treatment:** | Patients will receive the recommended dose of monotherapy of SCB01A for 9 weeks (3wk*3 cycles) or until disease progression, intolerable toxicity, consent withdrawal or death, whichever occurs first. |
| **Endpoints:** | Primary endpoint:<br>• DCR, defined as; complete response (CR) + partial response (PR) + stable disease (SD) at Week 9, according to RECIST v1.1 criteria<br>Secondary endpoints:<br>• PFS<br>• OS rate at 36 weeks after first treatment with SCB01A<br>• Safety: The safety endpoints used to achieve the secondary objectives of this study are:<br>o Hematology, clinical chemistry, coagulation factors and urinalysis laboratory data changes<br>o AE/SAE incidence<br>o Physical examination results changes<br>o Vital sign changes<br>o Electrocardiogram (ECG) (including PR, QRS, QT, QTc, and RR intervals) results<br>• Health outcomes assessment using patient-reported EORTC QLQ-C30 and H&N35 questionnaires. |
| **Criteria for Evaluation:** | Efficacy measurements:<br>*Tumor Measurement:*<br>Tumor response will be assessed by using computerized tomography (CT) or MRI scans according to RECIST v1.1 at baseline, and every 3 cycles prior to the next cycle until progression of the disease. For patients who meet DC criteria after the first 3 cycles of study treatment, additional radiological tumor assessments will be performed at Week 12.<br>Scans must include brain, chest, abdomen, and pelvis. The imaging technique used at baseline should be used throughout the study.<br>Patients will be considered evaluable for DCR in this study if they fulfill the criteria for evaluation according to RECIST v1.1, i.e., those patients who undergo a baseline disease assessment within 4 weeks of treatment initiation, and who undergo at least 1 disease assessment on the study.<br>• DCR is defined as the percentage of patients who have achieved CR, PR and SD at a particular time point after first treatment, according |

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| | to RECIST v1.1.<br>• PFS is defined as the time from the start of treatment up to the date of first progression based on RECIST v1.1, second primary malignancy or death from any cause, whichever occurs first.<br>• OS rate is defined as the percentage of patients who are still alive at a particular time point after first treatment with SCB01A<br>Survival data will be collected throughout the active treatment phase and during the 36 weeks follow-up period. Survival follow-up after patient 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 patients with measurable disease at baseline.<br><br><u>Dose Limiting Toxicity (DLT) (only in run-in phase)</u><br>• 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:<br>1. Grade 4 neutropenia exceeding 5 days' duration;<br>2. Grade 4 thrombocytopenia;<br>3. Grade 4 anemia;<br>4. Grade 3 or greater neutropenia with complications (e.g., fever, infection, etc.);<br>5. Grade 3 or greater thrombocytopenia with complications (e.g., bleeding);<br>6. 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;<br>7. Grade 3 or greater prolonged QTc interval;<br>8. Grade 3 or greater neurotoxicity;<br>9. Delayed treatment exceeding 14 days duration due to drug-related toxicity.<br><u>Safety measurements:</u><br>• Incidence and intensity of AEs evaluated using the CTCAE version 4.03<br>• Incidence and intensity of clinically significant abnormal laboratory values evaluated using the CTCAE version 4.03<br>• Percentage of patients experiencing dose modifications including delays or omissions or discontinuation of study medication<br>• Physical examination findings<br>• Vital signs measurements<br>• ECG (including PR, QRS, QT, QTc and RR intervals) findings |

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| | PK measurements:<br>• PK will be performed on patients enrolled in the run-in phase.<br>PK blood samples will be taken immediately pre-infusion then at 2, 3, 4, 6, 10, 21 and 24 hours after the start of infusion on Days 1 and 8 of Cycles 1, 2 and 3 (time window at each sample collected: ±5 min).<br>Bioanalytical measurements:<br>Exploratory research will be performed to analyze relevant biomarkers and the correlation with clinical outcome.<br>• Biomarkers analysis will be performed on patients enrolled in the run-in phase including circulating endothelial cells (CEC), vascular endothelial growth factor (VEGF) and circulating endothelial progenitor (CEP) cells<br>• Tumor micro vessel density and blood flow by dynamic contrast-enhanced MRI (DCE-MRI) will be performed in patients with identified sites which be selected by the sponsor at both baseline and 6 hours after the infusion of the drug on C1D1<br>• Human Papillomavirus (HPV) status (expression of p16 by immunohistochemistry [IHC]) at baseline for all patients. The sample could be collected from the previously adapted tissue.<br>Health outcomes measurements:<br>The following health outcomes assessments will be completed by patients:<br>• EORTC QLQ-C30, version 3;<br>• EORTC QLQ-H&N35<br>Health outcomes assessments will be performed at screening and before study drug administrated, except C1D1. |
| **Statistical Methods:** | Populations for Analysis<br>Patients will be categorized into the following populations for analysis:<br>• **FAS:** The FAS consists of all patients enrolled in the run-in phase who either completed at least 3 cycles of study treatment or experience a DLT, and all patients enrolled in the continuation phase (Phase II).<br>• **Per-protocol (PP) population**: The PP population will consist of all patients who completed at least 3 cycles of study treatment regimen defined for Phase II, have measurable baseline disease and, at least, one post-baseline RECIST assessment (PD, SD, PR or CR). Patients 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.<br>• **Safety population**: The safety population will consist of all patients who received, at least, one dose of SCB01A, and have at least one post-dose safety evaluation.<br>• **PK population:** The PK population will consist of all patients who received, at least, one dose of SCB01A with sufficient post-dose bio-samples collected for PK profile characterization (run-in phase |

only).

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 optimal two stage design[1,2]
- Type I error (one-sided): 10%
- Power: 80%
- Response probability of null hypothesis (P0): 0.10
- Response probability of SCB01A (P1): 0.25

According to these hypotheses, up to 64 patients need to be recruited into the study (including patients from the run-in phase). At least 6 patients are required to achieve CR, PR or SD at the end of the 9$^{th}$ week after first treatment with SCB01A for the study to meet its primary objective. The trial will be discontinued if DC is observed in one or none patients after the Stage 1Disease Controls Review.

**Stopping rule:** stopped early for futility if less than 2/13 (including 0 or 1 of 13 patients) show DCR in Stage 1 of Phase II with no further investigation of the drug if less than 6/34 achieve DCR by the end of Stage 2 of Phase II.

Both according to FAS and PP approaches (all enrolled patients who meet the eligibility criteria and do not present major deviations during the study) will be included in the analyses. The conclusion will be summarized according to analyses of PP population. Inferential analysis results will be expressed as point estimates and their 95% confidence intervals (CIs). To be consistent with the sample size calculation, the 90% CI will also be presented. Analyses will be carried out using SAS® Software, version 9.3 or higher (SAS Institute, Cary, North Carolina, USA).

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

PK Evaluations

The blood samples will be assayed for SCB01A and PK parameters (area under the plasma concentration-time curve from time zero to time t [$AUC_{0-t}$], area under the plasma concentration-time curve from time zero to infinite time [$AUC_{0-inf}$], and maximum plasma concentration [$C_{max}$], clearance [CL], volume of distribution [$V_d$], half-life [$t_{1/2}$], elimination

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| | constant [$K_{el}$], mean residence time [MRT] and time to maximum concentration [$T_{max}$]) will be determined and presented graphically and descriptively (as appropriate).<br><br>A detailed SAP will be finalized prior to final database lock. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and the Clinical Study Report. |
| **Duration of the Study** | The planned duration of the entire study is approximately 30 months with an enrolment period of 12 months. |
| **End of Study** | The study will be completed 36 weeks after the last patient receiving 1$^{st}$ treatment with SCB01A |

**Table 1: Study Schedule, Run-in phase (Dose 1, 0a, 1a, 2, 2a, 3, 3a, and 4 SCB01A)**

| Study Visit[1] | Screening | C1D1 | C1D8 | C1D15 | C2D1 | C2D8 | C2D15 | C3D1 | C3D8 | C3D15 | C4D1-CXD1[4] | C4D8-CXD8[4] | EOT/ Early With-drawal[2] | Follow-Up (Phone Call)[3] | Un-sche-duled |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Days** | **- 28 to -1** | **1 (±0)** | **8 (±1)** | **15 (±2)** | **22 (±1)** | **29 (±1)** | **36 (±2)** | **43 (±1)** | **50 (±1)** | **57 (±2)** | **64 (±1)** | **71 (±1)** | **NA** | **NA** | **NA** |
| **Activities** | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Eligibility Criteria | X | X | | | | | | | | | | | | | |
| Physical Examination | X | 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 | | X | X | | | |
| ECOG Performance Status | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Adverse Events Review[5] | X | X | X | 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 | X |
| 12-Lead ECG[6] | X | X | X | | X | X | | X | X | | X | X | X | | X[16] |
| Radiological Image Assessements[7] | X | | | | | | | | | | X | | X | | X[16] |
| Safety Laboratory | X | X[8] | X | X | X | X | X | X | X | X | X | X | X | | X[16] |
| Urinalysis | X | X[8] | | | X | | | X | | | X | | X | | X[16] |
| Serum Pregnancy Test[9] | X | | | | | | | | | | | | | | |
| Coagulation | | X[8] | X | X | X | X | X | X | X | X | X | X | X | | X[16] |
| HPV | X | | | | | | | | | | | | | | |
| Study Drug Administration | | X | X | | X | X | | X | X | | X | X | | | |
| EORTC Questionnaires[10] | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| PK[11] | | X | X | | X | X | | X | X | | | | | | |
| Biomarker[12] | | X | | | | | | | | X | | | | | |

| Study Visit[1] | Screening | C1D1 | C1D8 | C1D15 | C2D1 | C2D8 | C2D15 | C3D1 | C3D8 | C3D15 | C4D1-CXD1[4] | C4D8-CXD8[4] | EOT/ Early With-drawal[2] | Follow-Up (Phone Call)[3] | Un-sche-duled |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Days** | **- 28 to -1** | **1 (±0)** | **8 (±1)** | **15 (±2)** | **22 (±1)** | **29 (±1)** | **36 (±2)** | **43 (±1)** | **50 (±1)** | **57 (±2)** | **64 (±1)** | **71 (±1)** | **NA** | **NA** | **NA** |
| **Activities** | | | | | | | | | | | | | | | |
| DCE-MRI[13] | X | X | | | | | | | | | | | | | |
| Survival Status[14] | | | | | | | | | | | | | | X | |
| Cancer Therapy[15] | | | | | | | | | | | | | | X | |
| Nerve Conduction Velocity [17] | X | | | | | | | | | | | | | | |

[1] Patients 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.
[2] EOT visit should be conducted 21 ± 2 days after the last infusion. Early withdrawal visit should be conducted within 21 days after the patient received the last dose of study treatment.
[3] Follow-up visits will be performed after the patient 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.
[4] Starting from cycle 4, there will be no study visit on Day 15.
[5]All AEs including SAEs must be reported from the time of informed consent signed and must continue to be followed for 28 days after last administration of study treatment.
[6] ECG will be performed prior to study drug administration, within 1 hour following study drug administration, 2 hours after study drug administration, immediately after the 3 hour infusion, 4 hours after study drug administration, and 24 hours after administration of the study drug. Starting from Cycle 4, the ECG will be obtained at every treatment cycle within 1 hour following study drug administration and at EOT/early withdrawal visit (time window: ±5 min).
[7]Tumor assessments should be performed at baseline, and every 3 cycles prior to next cycle until progression of disease. For patients who meet DC criteria after the first 3 cycles of study treatment, additional radiological tumor assessments should be perfor med at Week 12. Any additional assessment can be arranged when clinically indicated.
[8] Test results within 7 days prior to Cycle 1, Day 1 (C1D1) are acceptable. Only items not performed or obtained within 7 days prior to C1D1 should be tested.
[9] Serum pregnancy test for women of childbearing potential must be performed ≤ 14 day prior to first dose.
[10] Quality of Life questionnaires (EORTC QLQ-C30 and H&N35) should be performed at Screening and all clinic visits (before study drug administered, where applicable, except at C1D1).
[11] PK blood samples will be taken immediately pre-infusion then at 2, 3, 4, 6, 10, 21 and 24 hours after start of infusion on Day 1 and Day 8 of Cycles 1, 2 and 3 (time window: ±5 min).
[12] Blood Sample for VEGF and CEC will be taken immediately pre-infusion then at 6, 10 and 24 hours after start of infusion on C1D1 and C3D15. Blood Samples for CEP will be taken immediately pre-infusion and C3D15.
[13] Tumor microvessel density and blood flow by DCE-MRI at both baseline (-28 to -1 Day) and 6 hours (+/- 1hour) after the infusion of the drug on C1D1.
[14] Follow-up for survival status will performed via telephone call if the site is unable to confirm via chart review or clinical visit.
[15]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.
[16] To be performed when necessary at the patient's request or per Investigator decision.
[17] To be performed for all patients at baseline and then during the trial only if grade 2 or above neurological symptoms experienced by the patient after receiving treatment with SCB01A.Refer section 5.9 for further details.

**Table 2: Study Schedule, Phase II, Stage 1 and Stage 2, Optimal dose SCB01A**

| Study Visit[1] | Screening | C1D1 | C1D8 | C1D15 | C2D1 | C2D8 | C2D15 | C3D1 | C3D8 | C3D15 | C4D1-CXD1[4] | C4D8-CXD8[4] | EOT/ Early With-drawal[2] | Follow-Up (Phone Call)[3] | Un-sche-duled |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Days** | **- 28 to -1** | **1 (±0)** | **8 (±1)** | **15 (±2)** | **22 (±1)** | **29 (±1)** | **36 (±2)** | **43 (±1)** | **50 (±1)** | **57 (±2)** | **64 (±1)** | **71 (±1)** | **NA** | **NA** | **NA** |
| **Activities** | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Eligibility Criteria | X | X | | | | | | | | | | | | | |
| Physical Examination | X | 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 | | X | X | | | |
| ECOG Performance Status | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Adverse Events Review[5] | X | X | X | 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 | X |
| 12-Lead ECG[6] | X | X | X | | X | X | | X | X | | X | X | X | | X[15] |
| Radiological Image Assessements[7] | X | | | | | | | | | | X | | X | | X[15] |
| Safety Laboratory | X | X[8] | X | X | X | X | X | X | X | X | X | X | X | | X[15] |
| Urinalysis | X | X[8] | | | X | | | X | | | X | | X | | X[15] |
| Serum Pregnancy Test[9] | X | | | | | | | | | | | | | | |
| Coagulation | | X[8] | X | X | X | X | X | X | X | X | X | X | X | | X[15] |
| HPV | X | | | | | | | | | | | | | | |
| Study Drug Administration | | X | X | | X | X | | X | X | | X | X | | | |
| EORTC Questionnaires[10] | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Biomarker[11] | | X | | | | | | | | X | | | | | |
| DCE-MRI[12] | X | X | | | | | | | | | | | | | |

| **Study Visit[1]** | **Screening** | **C1D1** | **C1D8** | **C1D15** | **C2D1** | **C2D8** | **C2D15** | **C3D1** | **C3D8** | **C3D15** | **C4D1-CXD1[4]** | **C4D8-CXD8[4]** | **EOT/ Early With-drawal[2]** | **Follow-Up (Phone Call)[3]** | **Un-sche-duled** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Days** | **- 28 to -1** | **1 (±0)** | **8 (±1)** | **15 (±2)** | **22 (±1)** | **29 (±1)** | **36 (±2)** | **43 (±1)** | **50 (±1)** | **57 (±2)** | **64 (±1)** | **71 (±1)** | **NA** | **NA** | **NA** |
| **Activities** | | | | | | | | | | | | | | | |
| Survival Status[13] | | | | | | | | | | | | | | X | |
| Cancer Therapy[14] | | | | | | | | | | | | | | X | |
| Nerve Conduction Velocity [16] | X[16] | | | | | | | | | | | | | | |

[1] Patients 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.
[2] EOT visit should be conducted 21 ± 2 days after the last infusion. Early withdrawal visit should be conducted within 21 days after the patient received the last dose of study treatment.
[3] Follow-up visits will be performed after the patient 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.
[4] Starting from cycle 4, there will be no study visit on Day 15.
[5]All AEs including SAEs must be reported from the time of informed consent signed and must continue to be followed for 28 days after last administration of study treatment.
[6] ECG will be performed prior to study drug administration, within 1 hour following study drug administration, 2 hours after study drug administration, immediately after the 3 hour infusion, 4 hours after study drug administration, and 24 hours after administration of the study drug. Starting from Cycle 4, the ECG will be obtained at every treatment cycle within 1 hour following study drug administration and at EOT/early withdrawal visit (time window: ±5 min).
[7]Tumor assessments should be performed at baseline, and every 3 cycles prior to next cycle until progression of disease. For patients who meet DC criteria after the first 3 cycles of study treatment, additional radiological tumor assessments should be perfor med at Week 12. Any additional assessment can be arranged when clinically indicated.
[8] Test results within 7 days prior to Cycle 1, Day 1 (C1D1) are acceptable. Only items not performed or obtained within 7 days prior to C1D1 should be tested.
[9] Serum pregnancy test for women of childbearing potential must be performed ≤ 14 day prior to first dose.
[10] Quality of Life questionnaires (EORTC QLQ-C30 and H&N35) should be performed at Screening and all clinic visits (before study drug administered, where applicable, except at C1D1).
[11] Blood Sample for VEGF and CEC will be taken immediately pre-infusion then at 6, 10 and 24 hours after start of infusion on C1D1 and C3D15. Blood Samples for CEP will be taken immediately pre-infusion and C3D15.
[12] Tumor microvessel density and blood flow by DCE-MRI at both baseline (-28 to -1 Day) and 6 hours (+/- 1hour) after the infusion of the drug on C1D1.
[13] Follow-up for survival status will performed via telephone call if the site is unable to confirm via chart review or clinical visit.
[14]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.
[15] To be performed when necessary at the patient's request or per Investigator decision.
[16] To be performed for all patients at baseline and then during the trial only if grade 2 or above neurological symptoms experienced by the patient after receiving treatment with SCB01A.Refer section 5.9 for further details.

# 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[3,4]. 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)*[3] . 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 cells[3].

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 patients 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 patient 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%) patients had stable disease (SD) for at least 2 cycles. s. Extended disease stabilizations were especially observed for 23 cycles in one patient with cholangiocarcinoma (4 mg/m$^2$) and 15 cycles in one patient with rectal cancer (3 mg/m$^2$) respectively, suggested that the most prominent SD patients remain in low dose (less than 6.5 mg/m$^2$).

A pre-clinical study demonstrated that SCB01A inhibited Detroit562 head and neck cell line proliferation. The inhibition concentration of 50% ($IC_{50}$) was 41 nM which is identical to the $IC_{50}$ of paclitaxel in our study. SCB01A was able to inhibit microtubule polymerization significantly under the concentration from 200 nM to 800 nM in 6 hours culture *in vitro*. Also, PK evidences suggested low dose SCB01A was following the one-compartment model, implying that 200 nM plasma concentrations will be enough to inhibit tumor growth. A pre-clinical study of SCB01A showed that the concentration at which tubulin inhibition occurred was 200 nM. Pharmacokinetic (PK) results demonstrated that average serum concentration of SCB01A reached 1000 nM at 24 mg/m$^2$ suggesting that the current dose is safe and beyond its probable efficacious concentration.. From pre-clinical toxicology study, the five days repeated doses of SCB01A showed no major toxicity in rat and dog models. These results support the treatment schedule for consecutive 5-days treatment every 3 weeks according to the International Conference on Harmonization (ICH) S9. The administration of SCB01A on Days 1 and 8 of a 3-week cycle applied in this Phase II study is below the maximum safety regimen suggested by regulatory guideline.

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 and 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 effect of SCB01A in patients with squamous cell carcinoma of head and neck who have failed previous platinum based therapies.

# 2. Study Objectives

## 2.1. Run-In Phase:

Primary Objective

To determine the optimal dose for 3 cycles of i.v. administration of SCB01A on Days 1 and 8 of each cycle in a 3-week cycle.

Secondary Objective**:**

To evaluate the safety and toxicity for 3 cycles of i.v. administration of SCB01A on Days 1 and 8 of each cycle in a 3-week cycle

## 2.2. Phase II:

**Primary Objective:**

To assess the disease control rate (DCR) at the end of the 9$^{th}$ week (3 cycles, each cycle consists of 21 days) after treatment with SCB01A, according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

**Secondary Objectives**

The secondary objectives of the study are listed below:

- To assess the overall survival rate at 36 weeks after treatment of SCB01A in patients with recurrent or metastatic squamous cell head and neck cancer who have previously been treated with platinum therapy.
- To assess the progression-free survival (PFS)
- To determine the recommended dose regimen of SCB01A for further investigation in different settings of head and neck squamous cell cancer.
- To assess the safety and toxicity profile of study treatment.
- To assess the PK profile of SCB01A of patients in the run-in phase.
- To assess health outcomes using patient-reported European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30) and EORTC QLQ H&N35 questionnaires.
- To assess biomarkers relevant to the efficacy and mechanism of action of SCB01A.
- To explore the possible association between biomarkers and clinical outcomes.

# 3. Investigational Plan

## 3.1. Description of Overall Study Design and Plan

This study is a single arm, open-label, Phase II trial. There will be two phases in this study, the run-in phase and the continuation phase (Phase II). Phase II will consist of 2 stages.

**Run-in Phase**

During the run-in phase, three patients will be enrolled and will receive 3 cycles of i.v. administration of SCB01A at a dose of 3.25 mg/$m^2$ on Days 1 and 8 of each cycle in a 3-week cycle (Dose 1). If one of the three patients experienced a Dose Limiting (DLT) during the first 3 cycles, an additional three patients will be enrolled at the same dose level (Dose 1). If ≤ 1of subjects experienced DLT at the given dose level, the dose of the subsequent cohort will be increased to the next level, then this process will continue until ≥ 2/3 or 2/6 of subjects experience DLT at certain dose level or the maximum dose( Dose 4) in this protocol, 24 mg/ $m^2$ is reached.

Rules for dose escalation for the run-in phase of the study are listed as following:

1. If 0/3 subjects have a DLT, escalate to the next higher dose level with a cohort of three subjects, unless the maximum dose to be tested in this study, i.e. 24 mg/$m^2$ (Dose 4). If 0/3 subjects have DLT in a cohort of 24 mg/$m^2$ (Dose 4), the 24 mg/$m^2$ (Dose 4) will be determined as the Optimal Dose.
2. If 1/3 subjects have DLT(s), enrol three more subjects at the same dose level:

a) If the dose for the cohort is less than 24 mg/$m^2$ (Dose 4) and 1/6 subjects have DLT(s), escalate to the next higher dose level;
b) If the dose for the cohort is higher than 3.5mg/$m^2$ (Dose 1) and > 1/6 subjects have a DLT, de-escalate to the next dose level (0a, 1a, 2a or 3a) with 3 subjects .
c) If >1 out of 6 subjects in the next lower dose (0a, 1a, 2a or 3a ) have DLT(s), then the previous dose will be defined as the MTD.
d) If ≤ 1 out of 6 subjects in the next lower dose (0a, 1a, 2a or 3a) have DLT(s), then that dose will be defined as the Optimal Dose.

3. If the dose for the cohort is 24 mg/$m^2$ (Dose 4) and 1≤/6 subjects have a DLT, then the dose level of 24 mg/$m^2$ (Dose 4) will be determined as the Optimal Dose.

Patients enrolled in the run-in phase must either complete 3 cycles of study treatment or experience a DLT to be included in the Full Analysis Set (FAS) for statistical analyses. During the run-in phase, patients who do not complete the 3 cycles of study treatment, and do not experience a DLT, will be replaced.

**Phase II (The continuation phase)**

After the Optimal Dose was determined in the run-in phase, a total number of 13 patients (including patients received Optimal Dose in the run-in phase) will be enrolled for stage 1 to receive 3 cycles of i.v. administration of SCB01A at Optimal Dose.

A safety committee review will be performed after stage 1 with the patients who completed 3 cycles of SCB01A treatment at the Optimal Dose. If more than two disease controls (DCs) are observed, another 21 patients will be enrolled into Stage 2 at the same dose level.

No patients will be replaced in the continuation phase (Phase II).

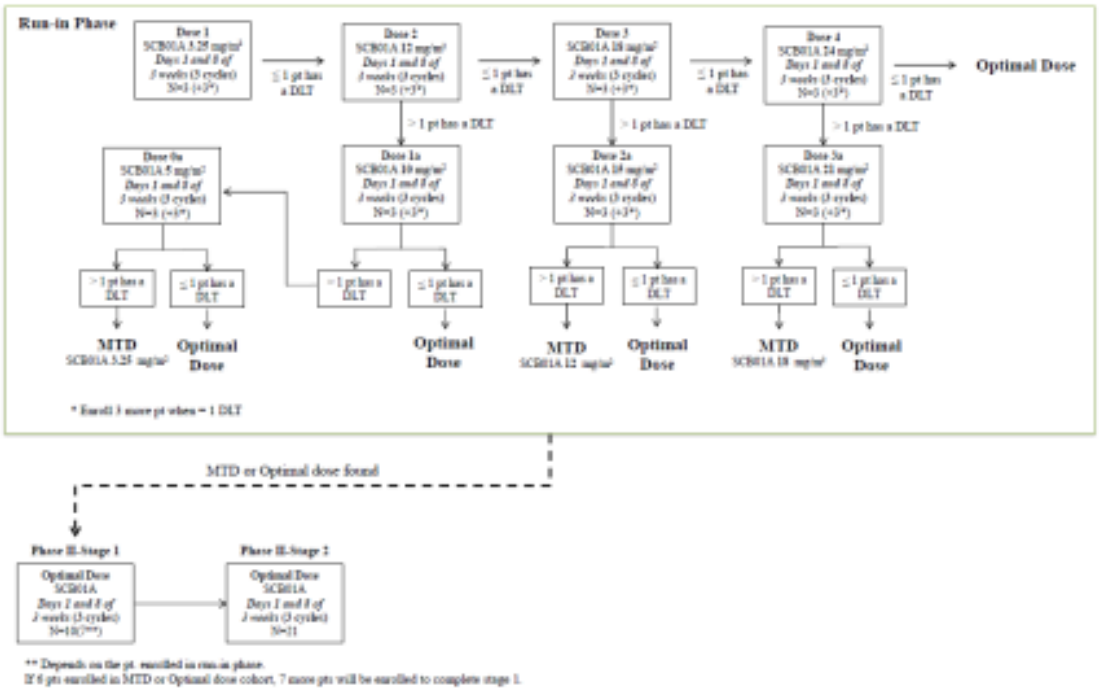


**Figure 2: Schematic Study Design**

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

The study will be terminated 36 weeks after the last patient has received their 1st treatment with SCB01A.

Safety monitoring committee:

A safety monitoring committee will be established to:

- Evaluate all AEs, and safety laboratory data for the run-in phase;

- Decide on the recommended dose regimen of SCB01A for Phase II.

The schedule of assessments for the run-in phase and Phase II, stages 1 and 2 is shown in detail in Table 1 and Table 2, respectively. The results of protocol specific assessments and procedures will be recorded in the source documents for the patients and on the appropriate page of the electronic case report form (eCRF). The different study days are described below.

## 3.2. Run-In 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
- Review of inclusion and exclusion criteria
- Initial history and pre-existing conditions
- Human Papillomavirus (HPV) status
- Historic illnesses
- Physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) performance status
- AEs
- Concomitant medication
- 12-lead ECG
- Tumor measurement
- Radiological imaging according to RECIST
- Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)
- Urinalysis
- EORTC QLQ-C30 and H&N35
- Laboratory tests (hematology, clinical chemistry and serum pregnancy test)
- Nerve Conduction Velocity (within 30 days before C1D1 for all subjects.)

### 3.2.2 Cycle 1, Day 1 (C1D1)

The following procedures/assessments will be performed:

- Review of inclusion and exclusion criteria
- Physical examination
- Vital signs
- Calculation of body surface area (BSA)
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG
- Urinalysis*
- Laboratory tests (hematology*, clinical chemistry* and coagulation)
- Study treatment infusion
- PK sampling
- Collection of blood samples for biomarkers (vascular endothelial growth factor [VEGF], circulating endothelial cells [CEC] and circulating endothelial progenitor [CEP] cells).
- DCE-MRI

  *Test results within 7 days are acceptable, only items not performed for screening within 7 days before this visit need to be tested again.
- Study Drug Administration

### 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
- Laboratory tests (hematology, clinical chemistry and coagulation)
- Study treatment infusion
- EORTC QLQ-C30 and H&N35
- PK sampling
- Study Drug Administration

### 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)
- EORTC QLQ-C30 and H&N35

### 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
- Urinalysis
- Laboratory tests (hematology, clinical chemistry and coagulation)
- Study treatment infusion
- EORTC QLQ-C30 and H&N35
- PK sampling
- Study Drug Administration

### 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 above)

### 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 above)

### 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 above).

#### 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 above)

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

The assessments on Day 15 of Cycle 3 is identical to Cycle 1, Day 15 and Cycle 2, Day 15 (see Section 3.2.4 above) and also includes collection of blood samples for biomarkers (VEGF, CEC and CEP)

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

Patients may continue with treatment of SCB01A at the same dose per investigator discretion if the patient is experiencing clinical benefit, 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 Sections 3.2.5 ) with the exception that no PK sampling will be performed.

Tumor assessment should be performed at baseline, and at the end of every 3 cycles which needs to be arranged within 5 days prior to the next cycle.

### 3.3. Phase II

During Phase II, Optimal Dose will be administered depending on the decision made by the safety committee. The Optimal Dose decided by safety committee, will be infused on Days 1 and 8 of each 3-week cycle as for the run-in phase. There will be no PK assessments to be performed in this phase.

#### 3.3.1 Screening Evaluations

The screening procedures/assessments will be performed within 28 days prior to Day 1 of Cycle 1 and are identical to the screening assessments performed before the run-in phase (see Section 0.1).

#### 3.3.2 Cycle 1, Day 1 (C1D1) (Optimal Dose))

The following assessments will be performed:

- Review of inclusion and exclusion criteria
- Physical examination
- Vital signs
- Calculation of BSA
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG
- Urinalysis*
- Laboratory tests (hematology*, clinical chemistry* and coagulation)

- Study treatment infusion
- DCE-MRI

*Test results within 7 days are acceptable, only items not performed for screening within 7 days before this visit need to be tested again.

- Study Drug Administration

#### 3.3.3 Cycle 1, Day 8 (C1D8) ±1 day (Optimal Dose)

The following assessments will be performed:

- Physical examination
- Vital signs
- Calculation of BSA
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG
- Laboratory tests (hematology, clinical chemistry and coagulation)
- Study treatment infusion
- EORTC QLQ-C30 and H&N35
- Nerve Conduction Velocity
- Study Drug Administration

#### 3.3.4 Cycle 1, Day 15 (C1D15) ±2 days (Optimal Dose)

The following assessments will be performed:

- Physical examination
- Vital signs
- ECOG performance status
- AEs
- Concomitant medication
- Laboratory tests (hematology, clinical chemistry and coagulation)
- EORTC QLQ-C30 and H&N35

#### 3.3.5 Cycle 2, Day 1 (C2D1) ±1 day (Optimal Dose)

The following assessments will be performed:

- Physical examination
- Vital signs
- Calculation of BSA
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG
- Urinalysis

- Laboratory tests (hematology, clinical chemistry and coagulation)
- Study treatment infusion
- EORTC QLQ-C30 and H&N35
- Study Drug Administration

#### 3.3.6 Cycle 2, Day 8 (C2D8) ±1 day (Optimal Dose)

The assessments on Day 8 of Cycle 2 is identical to Cycle 1, Day 8 (see Section 3.3.3 above)

#### 3.3.7 Cycle 2, Day 15 (C2D15) ±2 days ( Optimal Dose)

The assessments on Day 15 of Cycle 2 is identical to Cycle 1, Day 15 (see Section 3.3.4 above)

#### 3.3.8 Cycles >2, Day 1 ±1 day (Optimal Dose)

The assessments on Day 1 of Cycles >2 are identical to Cycle 2, Day 1 of Phase II (see Section 3.3.5 above) ).

#### 3.3.9 Cycles >2, Day 8 ±1 day ( Optimal Dose)

The assessments on Day 8 of Cycles >2 are identical to Cycle 1, Day 8 of Phase II (see Section 3.3.3 above).

#### 3.3.10 Cycles >2, Day 15 ±2 days ( Optimal Dose)

The assessments on Day 15 of Cycle 2 is identical to Cycle 1, Day 15 (see Section 3.3.4 above)

### 3.4. End of Treatment (EOT) Evaluation/Early Withdrawal

EOT visit should be conducted 21 ± 2 days after the last infusion. Early withdrawal visit should be conducted within 21 days after the patient 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)
- Urinalysis
- Laboratory tests (hematology, clinical chemistry and coagulation)
- EORTC QLQ-C30 and H&N35

## 3.5. Follow-up

After discontinuation of study treatment, all patients 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 until the end of the study.

## 3.6. 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)*
- Urinalysis*
- Laboratory tests (hematology, clinical chemistry and coagulation)

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

## 3.7. 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.

## 3.8. Selection of Study Population

### 3.8.1. 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;
4. Patients with non-resectable, unfeasible radiotherapy, recurrent or metastatic head and neck squamous cell carcinoma, after previous treatment with platinum agent;
5. At least one measurable tumor lesion as defined by RECIST version 1.1 as assessed by the investigator (local radiological image assessment);
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-2;
7. Life expectancy of 12 weeks or longer;
8. Patients must have radiological measurable or clinically evaluable disease. Physical examination and radiographic studies have to be performed within 28 days of enrolment;
9. Concurrent local therapy is not allowed, but concurrent palliative radiation

therapy to non-measurable sites of disease such as painful bone metastasis is permitted;

10. All eligible patients of childbearing potential have to use effective contraception; that is, double barrier contraceptive methods;
11. Documented progressive disease within past 6 months;
12. 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.
    h. Serum albumin ≥ 3 g/dL;
    i. INR ≤ 1.5 x ULN
    j. Total Bilirubin ≤ 1.5 x ULN

### 3.8.2. Exclusion Criteria:

1. Known primary CNS malignancy or CNS involvement (except for brain metastases that have been treated and are stable and patient is off steroids);
2. Chemotherapy, radiation therapy, major surgery or investigational agents less than 4 weeks prior to study drug treatment;
3. History of malignancy other than head and neck cancer. Second primary head and neck tumors are excluded with the exception of early stage non-melanoma skin cancer or carcinoma *in situ* of cervix;
4. Ultrasound or radiological evidence of liver cirrhosis;
5. Severe pulmonary obstructive or restrictive disease;
6. Uncontrolled inflammatory disease (autoimmune or infectious);
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. Participation in another clinical trial or treatment with any investigational drug within 30 days prior to study entry;
11. QTc > 450 msec;
12. Pregnant or breast-feeding patients, and men and women of child-bearing potential not using effective contraception while on study treatment;Known hypersensitivity to any component of SCB01A;
13. History of exposure to SCB01A or its analogues;
14. 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;

15. Any other reason the investigator deems the patient to be unsuitable for the study.

### 3.9. Removal of Patients from Treatment or Assessment

#### 3.9.1. 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 patients.

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

#### 3.9.2. Early Discontinuation of Individual Patients

The investigator may remove a patient 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
- Patient decides to discontinue study therapy
- Any medically appropriate reason or significant protocol violation, in the opinion of the investigator
- Lost follow-up

Patients may decide to discontinue study treatment for any reason. Patients 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, patients may elect to withdraw consent and decline further participation in the trial.

All patients 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 patient's discontinuation of study treatment and record this information on the eCRF. Patients 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 composed of absolute EtOH, PEG 300, and Solutol®. 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$^{o}$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 < 30 $^{o}$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/vials. The injection volume of SCB01A should be calculated based on the BSA of the subject. (See section 5.1.3). 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 over a period of 3 hours by i.v. infusion through a central line in order to avoid potential extravasation and tissue necrosis. 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 boxes of 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 Patients to Treatment Groups

There is no randomization to be done. All patients will receive the study drug, and the dose is dependent upon the phases of the study to which the patient is enrolled. Patients will be assigned to Dose 1 initially when they enter the run-in phase of the study. Dose selection for the Phase II will be based on the occurrence of DLTs during the run-in phase and the decision made by the safety committee.

### 4.7. Selection of Doses in the Study

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

## 4.8. Selection and Timing of Dose for each Patient

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

Patients entered into the run-in phase will be allocated to Dose 1 to Dose 4. Dose selection for Phase II will be based on the occurrence of DTLs during the run-in phase and the decision made by safety committee on the Optimal Dose for the Phase II (see Section 3.1).

*Dose 1:* one i.v. administration of 3.25 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or

*Dose 0a:* one i.v. administration of 5 mg/m$^2$ SCB01A on Day 1 and Day 8 of a 3-week cycle.

*Dose 1a:* one i.v. administration of 10 mg/m$^2$ SCB01A on Day 1 and Day 8 of a 3-week cycle.

*Dose 2:* one i.v. administration of 12 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or

*Dose 2a:* one i.v. administration of 15 mg/m$^2$ SCB01A on Day 1 and Day 8 of a 3-week cycle

*Dose 3:* one i.v. administration of 18 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or

*Dose 3a:* one i.v. administration of 21 mg/m$^2$ SCB01A on Day 1 and Day 8 of a 3-week cycle

*Dose 4:* one i.v. administration of 24 mg/m$^2$ SCB01A on Days 1 and 8 of a 3-week cycle; or

## 4.9. Dose Adjustment and Toxicity Management

There is no dose adjustment envisaged in this study. Where 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 $\leq 1$ 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 patient should be followed-up for survival analysis until the end of the study.

## 4.10. Blinding

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

## 4.11. Prior and Concomitant Therapy

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins, dietary supplements, and oral herbal preparations.

All medications that are taken by, or being administered to, the patient at the time of the Screening Visit, within 30 days prior to the Screening Visit, and for the duration of the study will be recorded in the eCRF.

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

Patients 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 eCRF

1. Any study participant that has had 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.
3. Therapy with anticoagulants, antiplatelet treatments (e.g. warfarin, heparins) are not allowed during the study

### 4.13. Treatment Compliance

Patients 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 eCRF.

# 5. Study Assessments and Procedures

## 5.1. Safety Procedures and Assessments

### 5.1.1. 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.

| | |
|---|---|
| Cardiovascular | Lymphatic |
| Respiratory | Hematologic |
| Gastrointestinal | Immunologic |
| Renal | Dermatologic |
| Hepatic | Psychiatric |
| Neurological | Genitourinary |
| Endocrine | Other |

### 5.1.2. 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:

- Height (cm) (only performed at baseline)
- Weight (kg) at each visit before a study treatment infusion
- 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 patient; i.e., the abnormality is clinically significant.

### 5.1.3. BSA Calculation

BSA will be calculated on dosing days, using the formula below[5]:

BSA ($m^2$) = [Height (cm) x Body Weight (kg)/3600]½

The total dose (mg) will be calculated as: Total Dose 1/Dose 2 ($mg/m^2$) x BSA ($m^2$)

### 5.1.4. Vital Signs

Vital signs will be obtained at baseline, clinic visits prior to study drug administration, if applicable and at the EOT/Early Withdrawal visit.

Vital signs will include heart rate, blood pressure, respiratory rate, and body temperature. Respiratory rate, heart rate and blood pressure (systolic/diastolic) will be obtained after the patient has been at rest for at least 5 minutes in a sitting position.

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.

## 5.2. ECOG Performance Status

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

**Table 3: ECOG Performance Status Scale[6]**

| 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. |

## 5.3. 12-lead ECG

During the run-in phase, the 12-lead ECG will be obtained prior to study drug administration, within 1 hour following study drug administration, 2 hours after study drug administration, immediately after the 3 hour infusion, 4 hours after study drug administration, and 24 hours after administration of the drug. After cycle 4, the ECG will be obtained at every treatment cycle within 1 hour following study drug administration, and EOT/early withdrawal visit (time window: ±5 min).

During Phase II (stage 1 and 2), the 12-lead ECG will be obtained at every treatment cycle within 1 hour following study drug administration and at EOT/Early Withdrawal visit.

The allowed time window for each ECG assessment is ±5 min. ECGs will be obtained whenever deemed necessary at the investigator's discretion. The following ECG measurements will be recorded in the patient's source documents and on the appropriate page(s) of the eCRF:

- QRS interval
- PR interval
- QT interval
- QTc interval
- RR 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).

## 5.4. DCE-MRI

Tumor micro vessel density and blood flow by DCE-MRI for the patients with identified sites at both baseline and 6 hours after the 1st infusion of the drug in C1D1.

## 5.5. Safety 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 and clinical chemistry blood samples will be obtained at screening, all clinic visits and the EOT/Early Withdrawal visit. Coagulation will be determined at all clinic visits (excluding screening). During the run-in phase minimum of 19 samples (180 ml) will be take. The number of sample might 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>
WBC with differential, red blood cell (RBC), hematocrit (Hct), Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count

<u>Clinical Chemistry</u>
Blood urea nitrogen (BUN), Creatinine, AST, ALT, ALP, Total Bilirubin, Albumin, Calcium, Glucose, Uric Acid, Potassium, Total creatine kinase (Ck) (if total Ck is above the ULN for the laboratory, Troponin-T or Troponin-I will be determined), gamma-glutamyl transferase (GGT). Total cholesterol, high-density lipoprotein

(HDL), low-density lipoprotein (LDL), triglycerides (TG), amylase and lipase will be tested at the Screening Visit.

Coagulation
PT, INR

Urinalysis
Specific gravity, pH, protein, glucose, leucocytes, erythrocyte, nitrite, ketone, urobilinogen, bilirubin and sediment including RBC, WBC, Hyaline, Cast, CAOX, Crystal, AMOR and mucus.

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.

## 5.6. Bioanalytical Assessments

PK Procedures

PK will be performed on patients enrolled in the run-in phase.
PK blood samples will be taken immediately pre-infusion then at 2, 3, 4, 6, 10, 21 and 24 hours after start of infusion on Days 1 and 8 of Cycles 1, 2 and 3 (time window at each sample collected: ±5 min). Sixteen (16) samples (10 mL) per cycle will be taken (480 mL during 3 cycles of the run-in phase). Also see Section 6.4 for more detail.

Biomarkers

Blood samples (10 mL) will be collected for biomarkers analysis on patients enrolled in the run-in phase; including CEC, VEGF and CEP cells.

Blood samples for biomarkers will be taken immediately pre-infusion then at 6, 10 and 24 hours after start of infusion on Day 1 of Cycle 1 and one sample during the clinic visit on Day 15 of Cycle 3 (5 samples per cycle). VEGF and CEC will be analyzed for all time points that samples were taken and CEP will be analyzed only from pre-infusion sample and the Day 15 Cycle 3 sample.

## 5.7. EORTC QLQ-C30

Patients will complete the questionnaire at Screening and before study drug administered, except C1D1.

The questionnaire consists of 65 questions that help determine the health outcome of the patients.

## 5.8. EORTC QLQ H&N35

Patients will complete the questionnaire at Screening and before study drug administered, except C1D1.

### 5.9. Nerve Conduction Velocity

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

a. Baseline: within 30 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;
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 every 3 cycles prior to next cycle until progression of disease. For patients who meet DC criteria after the first 3 cycles of study treatment, additional radiological tumor assessments should be performed at Week 12. 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.

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

### 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 during the run-in phase, 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.

### 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 patients experiencing dose adjustments, including delays or discontinuation of study medication
- Physical examination findings
- Vital signs measurements
- ECG (including PR, QRS, QT, QTc and RR intervals) findings

### 6.4. Pharmacokinetic Measurements

PK will be performed on patients enrolled in the run-in phase.

- PK blood samples will be taken immediately pre-infusion then at 2, 3, 4, 6, 10, 21 and 24 hours after start of infusion on Days 1 and 8 of Cycles 1, 2 and 3 (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.

### 6.5. Bioanalytical Measurements

Exploratory research will be performed to analyze relevant biomarkers and the correlation with clinical outcome.

- Biomarkers analysis will be performed on patients enrolled in the run-in phase, including CEC, VEGF and CEP cells)
- Tumor micro vessel density and blood flow by DCE-MRI will be performed in the patients with identified sites at both baseline and at 6 hours after the infusion of the drug on C1D1
- HPV status (expression of p16 by immunohistochemistry [IHC]) at baseline for all patients

### 6.6. Health outcomes measurements

The following health outcomes assessments will be completed by patients (see Section 11.3 [Appendix 4]):

- EORTC QLQ-C30), version 3;
- EORTC QLQ-H&N35

Health outcomes assessments will be performed at screening and all clinic visits (before study drug administered, where applicable, except at C1D1)

# 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 patient 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 eCRF 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 patient’s daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient’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

- **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 informed consent obtained until 28 days after the last dose of study treatment) observed by the Investigator or reported by the patient (whether or not attributed to study drug), will be reported on the eCRF. 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 patient's permanent withdrawal of IP or from the study will be discussed between the investigator and medical monitor. The eCRF 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 patient's removal from study treatment. A patient may also voluntarily withdraw from study treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the patient 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 patient 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 patient 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 fulfil 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 patient'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 (patient 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 patient or study patient's partner becomes or is found to be pregnant during the study patient'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 patient 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 databased lock. Any significant changes to the analyses described in this protocol will be highlighted 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[1,2]
- Type I error (one-sided): 10%
- Power: 80%
- Response probability of null hypothesis (P0): 0.10
- Response probability of SCB01A (P1): 0.25

According to these hypotheses, up to 58 patients need to be recruited into the study (including patients from the run-in phase). At least 6 patients are required to achieve complete response (CR), PR or SD at the end of the 9$^{th}$ week after first treatment with SCB01A for the study to meet its primary objective. The trial will be discontinued if DC is observed in two or fewer patients after the Stage 1 interim analysis review.

## 8.3. Populations for Analysis

Patients will be categorized into the following populations for analysis:

FAS: The FAS consists of all patients enrolled in the run-in phase who either completed at least 3 cycles of study treatment or experience a DLT, and all patients enrolled in the continuation phase (Phase II).

Per-protocol (PP) population: The PP population will consist of all patients who completed at least 3 cycles of study treatment regimen defined for Phase II, have measurable baseline disease and at least one post-baseline RECIST assessment (PD, SD, PR or CR). Patients 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.

Safety population: The safety population will consist of all patients who received at least one dose of SCB01A, and have at least one post-dose safety evaluation.

PK population: The PK population will consist of all patients who received at least one dose 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.

- Hematology, clinical chemistry, coagulation factors and urinalysis laboratory data changes
- AE incidence/SAE incidence
- Physical examination result changes
- Vital sign changes
- Electrocardiogram (ECG) (including PR, QRS, QT, QTc, and RR intervals) results

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 patients 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 patients who withdrew/stopped dosing will be tabulated. Number and percentage of patients 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 patients 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 DCR and secondary efficacy analysis will be performed to assess the PFS and overall survival rate.

Patients will be considered evaluable for DCR in this study if they fulfill the criteria for evaluation according to RECIST v1.1, i.e., those patients who undergo a baseline disease assessment within 4 weeks of treatment initiation, and who undergo at least 1 disease assessment on-study:

- DCR is defined as the percentage of patients who have achieved CR, PR and SD 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, second primary malignancy or death from any cause, whichever occurs first.
- Overall survival rate is defined as the percentage of patients who are still alive at 36 weeks after first treatment with SCB01A.

Inferential analysis results will be expressed as point estimates and their 95% CIs. To be consistent with the sample size calculation, the 90% CI will also be presented for the primary endpoint. Analyses will be carried out using SAS® Software, version 9.3 or higher (SAS Institute, Cary, North Carolina, USA).

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

The study will be stopped early for futility if less than three DCRs are observed following the completion of the first stage of Phase II. In addition, no further investigation of the drug will be pursued if less than 6 patients achieve DCR by the end of Stage 2 of Phase II.

## 8.6. PK Analysis

The blood samples will be assayed for SCB01A and PK parameters (area under the plasma concentration-time curve from time zero to time t [$AUC_{0-t}$], area under the plasma concentration-time curve from time zero to infinite time [$AUC_{0-inf}$], and 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. Health Outcomes Assessments

Health outcomes assessment using EORTC QLQ C30 and H&N35 questionnaires and will be completed by patients at time points specified in Table 1 and Table 2. Questionnaire data will be listed and summarized by dose group, cycle and day within cycle as applicable and may be presented graphically.

### 8.8. Interim Analysis

An interim statistical analysis will be performed following the completion of stage 1, Phase II. If more than two DCs are observed, an additional 21 patients will be enrolled into Stage 2 at the same dose level. The study will be stopped early for futility if less than 3 DCRs are observed following the completion of the first stage of Phase II with no further investigation of the drug if less than 6/34 achieve DCR by the end of Stage 2 of Phase 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 in Tokyo, Japan in 1975; Venice, Italy in 1983; Hong Kong in 1989; Somerset West, South Africa in 1996, and in Edinburgh, Scotland in 2000; notes of clarification were added in 2002 and 2004 (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 patient informed consent forms (ICFs) and other information for the patients, 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 patient 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. Patient Information and Consent

The investigator must fully inform the patient 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 patient 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 patient and one copy must be retained in the investigator's study records.

## 9.4. Confidentiality and Disclosure

Data on patients collected on eCRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, 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 patients. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a patient 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 eCRFs will be completed as soon as possible after the patient's visit. Corrections to data on the source will be documented. The investigator will review eCRFs 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 eCRFs for each patient 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 (eg, US FDA) upon request. A file for each patient must be maintained that includes the signed ICF and copies of all source documentation related to that patient. The investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

Patient identity information recorded will be maintained for at least 15 years on the patient 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 eCRFs.

The investigator will make available source documents, medical records, and source data necessary to complete eCRFs 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 patient 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 eCRF 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] Jung SH et al., 2004. Admissible two-stage designs for phase II cancer clinical trials, *Statistics in Medicine* 23:561-569.
[3] 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.
[4] Tozer, GM., Kanthou, C., & Baguley, BC. Disrupting tumor blood vessels. *Nat Rev Cancer.* 2005; 5(6): 423-435.
[5] Mosteller RD. "Simplified calculation of body-surface area". *N Engl J Med* 1987; 317:1098. PMID 3657876.
[6] 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** | **Strong** |
| fluvoxamine | bupropion |
| ciprofloxacin | cinacalcet |
| | fluoxetine |
| **Weak** | paroxetine |
| cimetidine | quinidine |
| | |
| **Others** | **Moderate** |
| amiodarone | duloxetine |
| efavirenz | sertraline |
| fluoroquinolones | terbinafine |
| fluvoxamine | |
| furafylline1 | **Weak** |
| interferon | amiodarone |
| methoxsalen | cimetidine |
| mibefradil | |
| ticlopidine | **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 Patients

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; the 35th WMA General Assembly, Venice, Italy, October 1983; the 41st WMA General Assembly, Hong Kong, September 1989; the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. A note of clarification on Paragraph 29 was added by the 54th WMA General Assembly, Washington, 2002; and a note of clarification on Paragraph 30 was added by the 56th WMA General Assembly, Tokyo, 2004.

### A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human patients. Medical research involving human patients includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association 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 only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human patients.
5. In medical research on human patients, considerations related to the well-being of the human patient should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human patients is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is patient to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need

special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be patient to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human patients in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human patients set forth in this Declaration.

**B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human patient.
11. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human patients should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest and incentives for patients.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human patients should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human patient must always rest with a medically qualified person and never rest on the patient of the research, even though the patient has given

consent.

16. Every medical research project involving human patients should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the patient or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human patients unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human patients should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the patient. This is especially important when the human patients are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The patients must be volunteers and informed participants in the research project.
21. The right of research patients to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the patient, the confidentiality of the patient's information and to minimize the impact of the study on the patient's physical and mental integrity and on the personality of the patient.
22. In any research on human beings, each potential patient 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. The patient should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the patient has understood the information, the physician should then obtain the patient's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the patient is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research patient who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed

consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a patient deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research patients with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research patients.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the

patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

[1] **Note of clarification on Paragraph 29 of the WMA Declaration of Helsinki**: The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method; or where a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition, and the patients who receive placebo will not be patient to any additional risk or serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] **Note of clarification on Paragraph 30 of the WMA Declaration of Helsinki:** The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic, and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

## 11.3. Appendix 3– Questionnaires EORTC QLQ C30 and QLQ H&N35

# EORTC QLQ C30

ENGLISH

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

ENGLISH

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |





QLQ H&N35

ENGLISH

## EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 31. | Have you had pain in your mouth? | 1 | 2 | 3 | 4 |
| 32. | Have you had pain in your jaw? | 1 | 2 | 3 | 4 |
| 33. | Have you had soreness in your mouth? | 1 | 2 | 3 | 4 |
| 34. | Have you had a painful throat? | 1 | 2 | 3 | 4 |
| 35. | Have you had problems swallowing liquids? | 1 | 2 | 3 | 4 |
| 36. | Have you had problems swallowing pureed food? | 1 | 2 | 3 | 4 |
| 37. | Have you had problems swallowing solid food? | 1 | 2 | 3 | 4 |
| 38. | Have you choked when swallowing? | 1 | 2 | 3 | 4 |
| 39. | Have you had problems with your teeth? | 1 | 2 | 3 | 4 |
| 40. | Have you had problems opening your mouth wide? | 1 | 2 | 3 | 4 |
| 41. | Have you had a dry mouth? | 1 | 2 | 3 | 4 |
| 42. | Have you had sticky saliva? | 1 | 2 | 3 | 4 |
| 43. | Have you had problems with your sense of smell? | 1 | 2 | 3 | 4 |
| 44. | Have you had problems with your sense of taste? | 1 | 2 | 3 | 4 |
| 45. | Have you coughed? | 1 | 2 | 3 | 4 |
| 46. | Have you been hoarse? | 1 | 2 | 3 | 4 |
| 47. | Have you felt ill? | 1 | 2 | 3 | 4 |
| 48. | Has your appearance bothered you? | 1 | 2 | 3 | 4 |

Please go on to the next page

ENGLISH

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 49. | Have you had trouble eating? | 1 | 2 | 3 | 4 |
| 50. | Have you had trouble eating in front of your family? | 1 | 2 | 3 | 4 |
| 51. | Have you had trouble eating in front of other people? | 1 | 2 | 3 | 4 |
| 52. | Have you had trouble enjoying your meals? | 1 | 2 | 3 | 4 |
| 53. | Have you had trouble talking to other people? | 1 | 2 | 3 | 4 |
| 54. | Have you had trouble talking on the telephone? | 1 | 2 | 3 | 4 |
| 55. | Have you had trouble having social contact with your family? | 1 | 2 | 3 | 4 |
| 56. | Have you had trouble having social contact with friends? | 1 | 2 | 3 | 4 |
| 57. | Have you had trouble going out in public? | 1 | 2 | 3 | 4 |
| 58. | Have you had trouble having physical contact with family or friends? | 1 | 2 | 3 | 4 |
| 59. | Have you felt less interest in sex? | 1 | 2 | 3 | 4 |
| 60. | Have you felt less sexual enjoyment? | 1 | 2 | 3 | 4 |

| During the past week: | | No | Yes |
|---|---|---|---|
| 61. | Have you used pain-killers? | 1 | 2 |
| 62. | Have you taken any nutritional supplements (excluding vitamins)? | 1 | 2 |
| 63. | Have you used a feeding tube? | 1 | 2 |
| 64. | Have you lost weight? | 1 | 2 |
| 65. | Have you gained weight? | 1 | 2 |